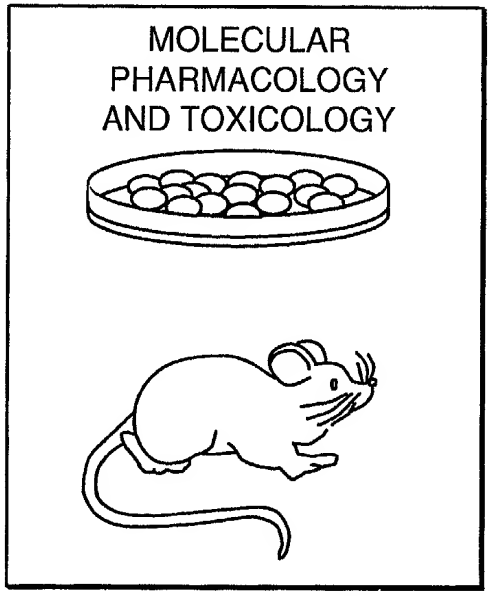
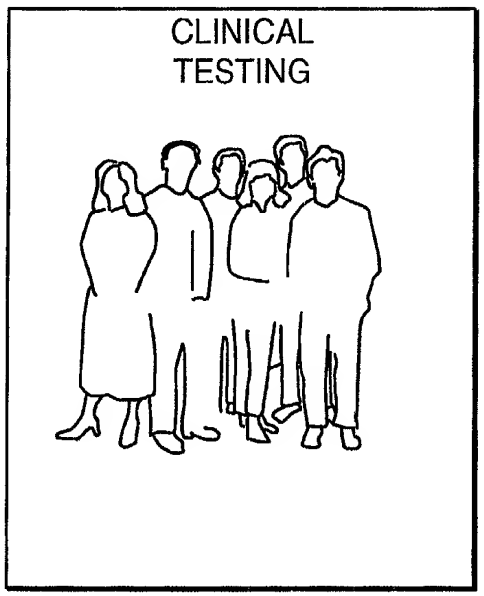
PRODUCT CANDIDATE PROFILES



- 25 TO 100 GENES
- MULTIPLE CELLS / ORGANS

BETTER PRODUCT CANDIDATES

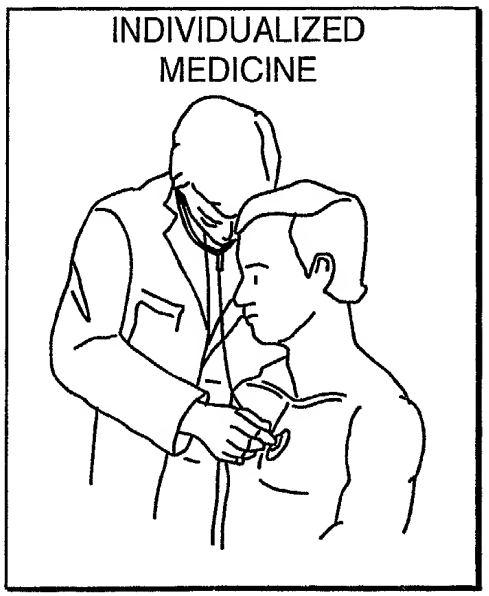
CLINICAL SURROGATE MARKER PROFILES



- 5 TO 15 GENES
- SMALL BLOOD SAMPLES

ACCURATE CLINICAL DEVELOPMENT

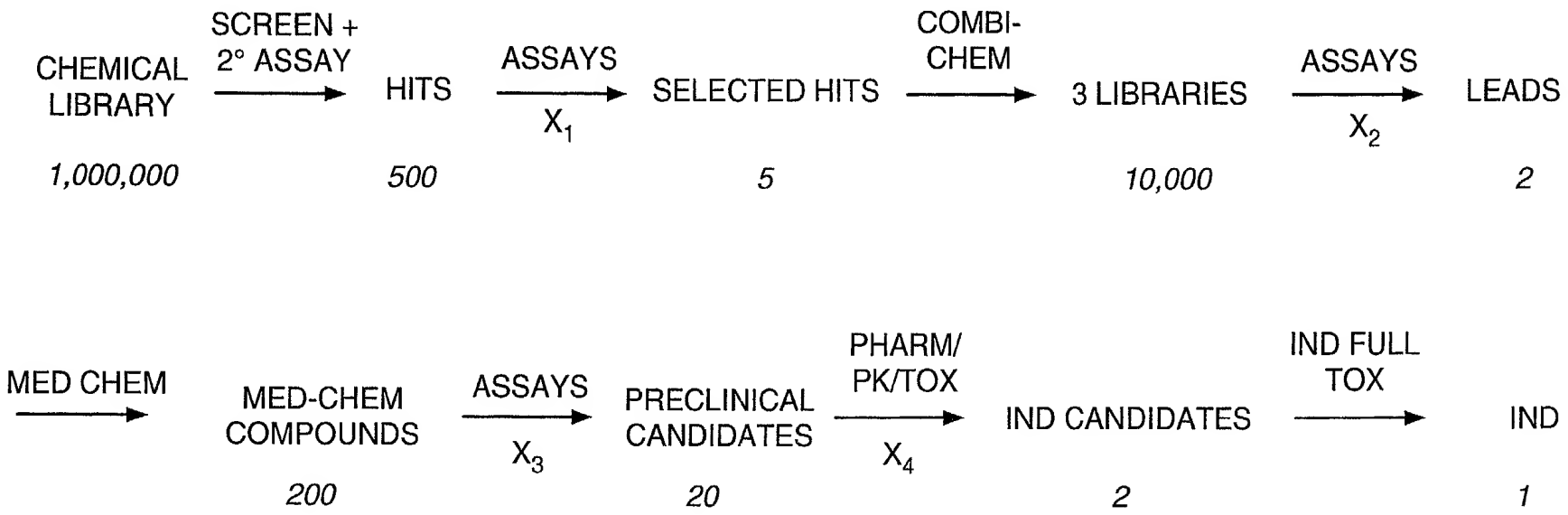
HEALTH PROFILES



- 100 TO 500 GENES
- SMALL BLOOD SAMPES

BETTER HEALTH CARE MANAGEMENT

FIG. 1



X_1, X_2, X_3 = PHYSIOCHEMICAL ANALYSIS
IN VITRO TOXICOLOGY
GENE EXPRESSION PROFILING

X_4 = IN VIVO GENE PROFILING

X_5 = SURROGATE MARKER

FIG. 2

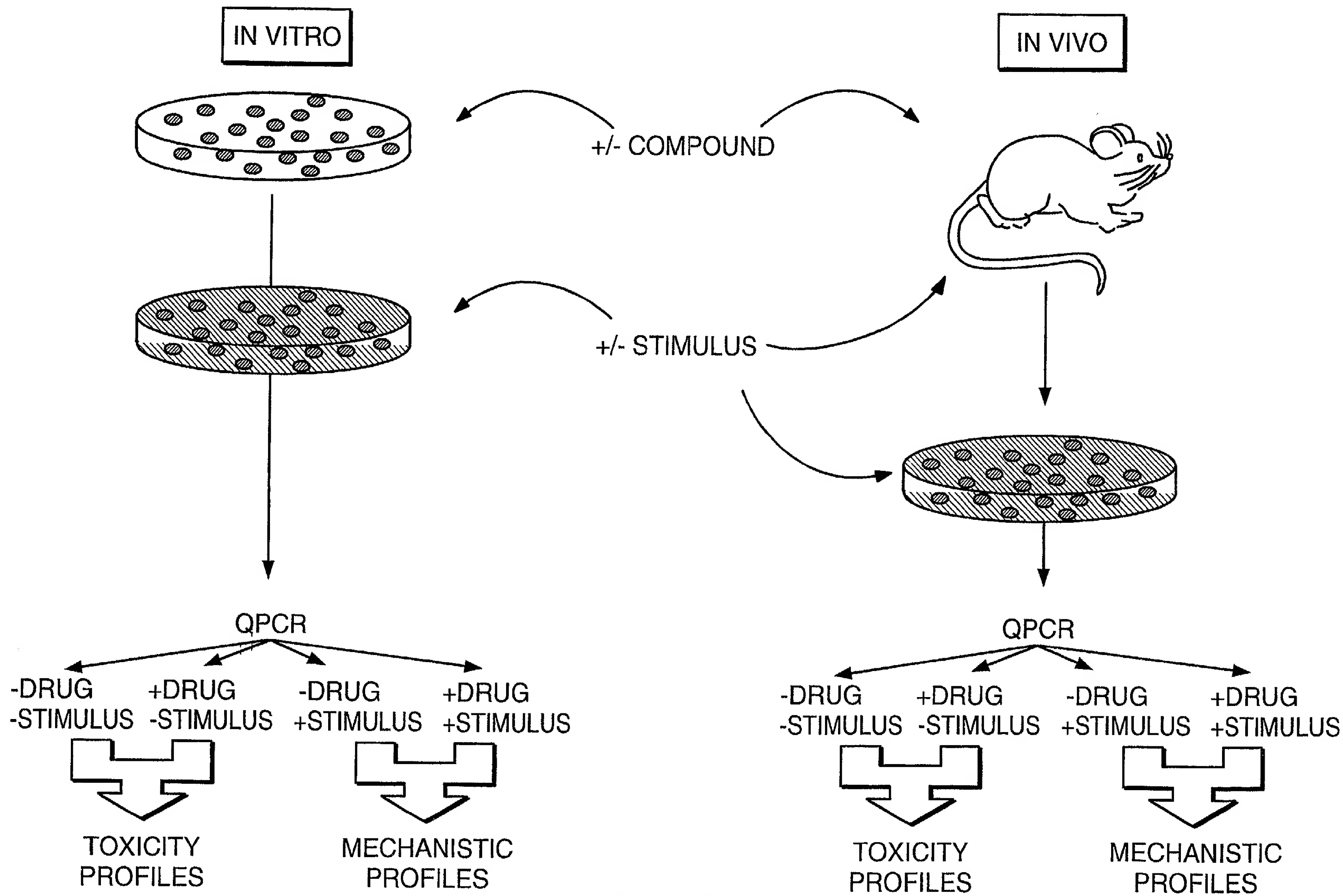


FIG. 3

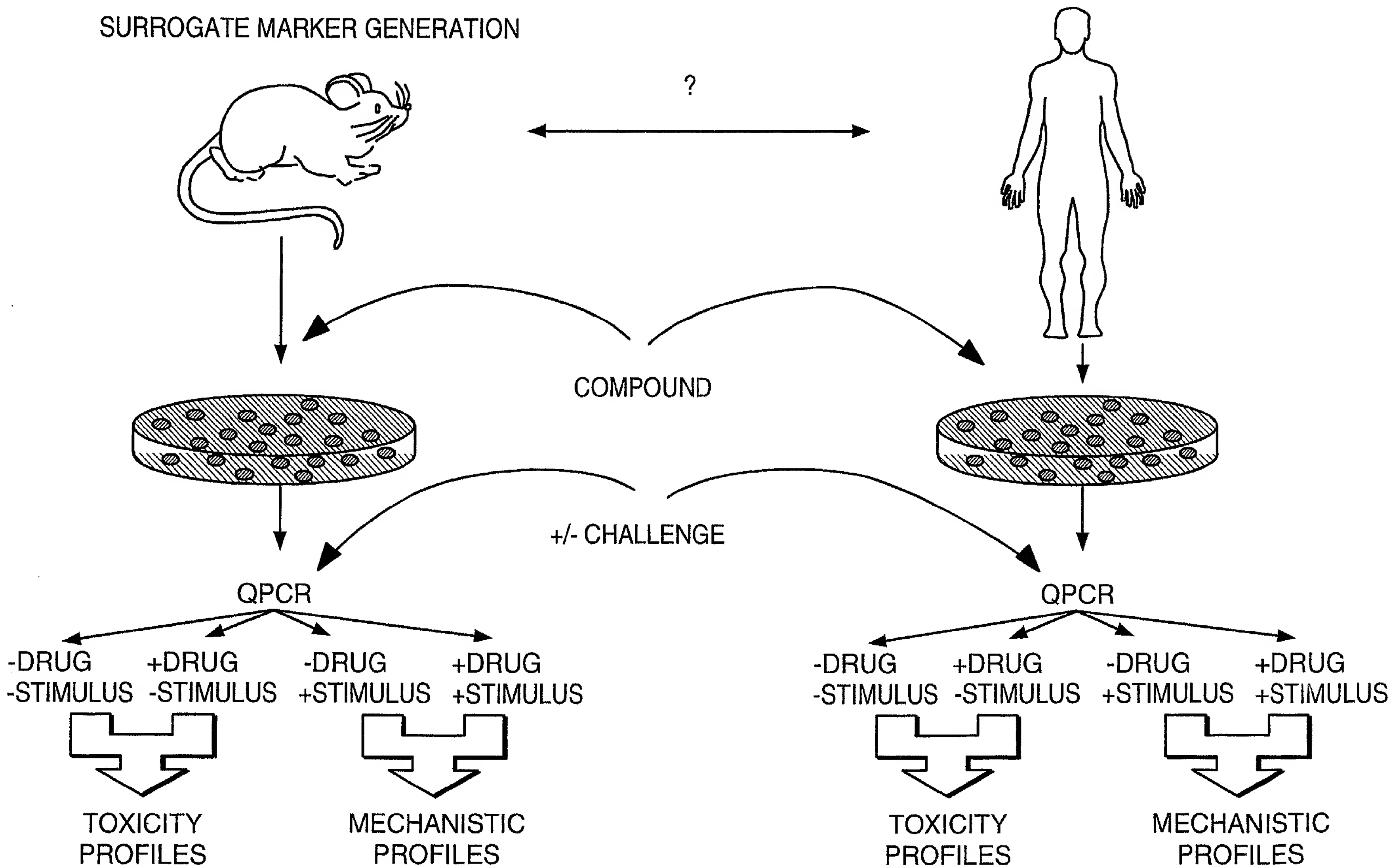
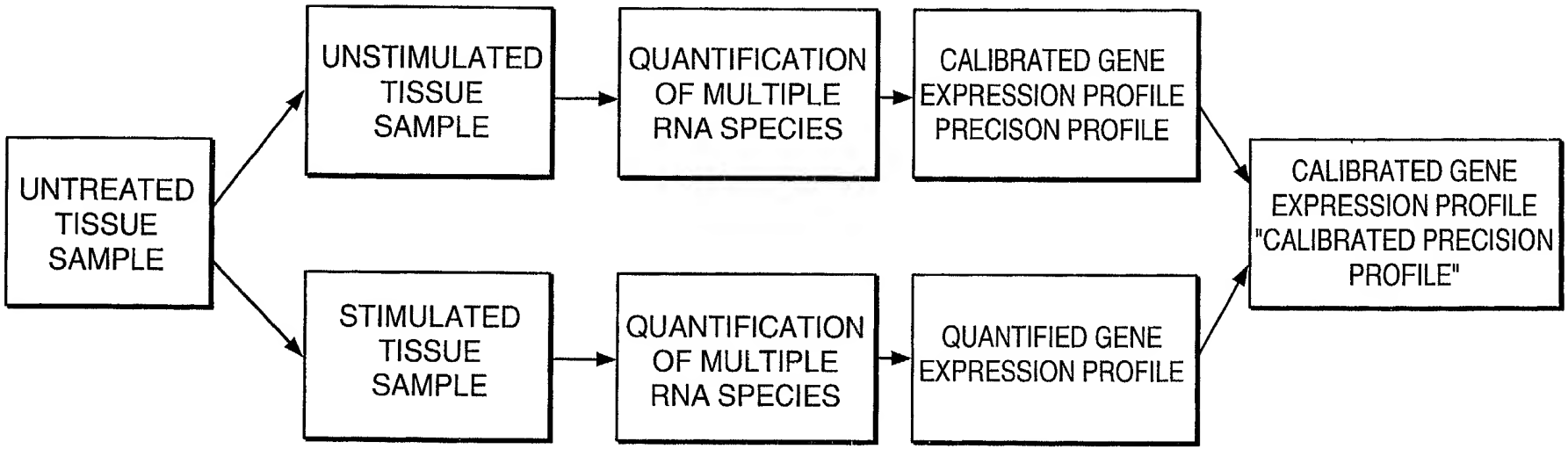

SURROGATE MARKER GENERATION
?
COMPOUND
+/- CHALLENGE
QPCR
-DRUG
-STIMULUS
+DRUG
-STIMULUS
-DRUG
+STIMULUS
+DRUG
+STIMULUS
TOXICITY
PROFILES
MECHANISTIC
PROFILES
QPCR
-DRUG
-STIMULUS
+DRUG
-STIMULUS
-DRUG
+STIMULUS
+DRUG
+STIMULUS
TOXICITY
PROFILES
MECHANISTIC
PROFILES

FIG. 4

PRODUCING A "CALIBRATED PRECISION PROFILE"



SOURCE PRECISION MEDICINE

FIG. 5

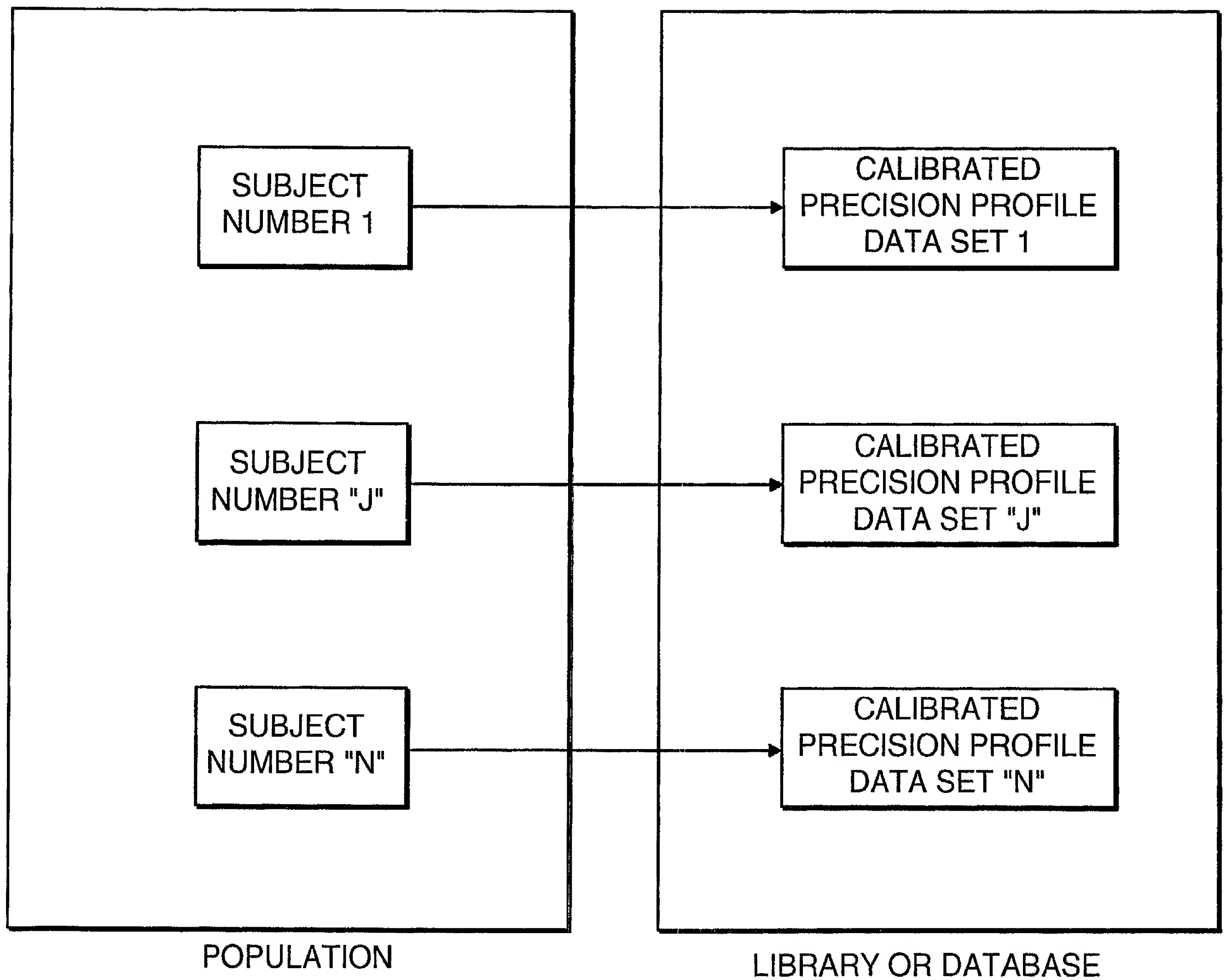

SUBJECT NUMBER 1
SUBJECT NUMBER "J"
SUBJECT NUMBER "N"
POPULATION
CALIBRATED PRECISION PROFILE DATA SET 1
CALIBRATED PRECISION PROFILE DATA SET "J"
CALIBRATED PRECISION PROFILE DATA SET "N"
LIBRARY OR DATABASE

FIG. 6

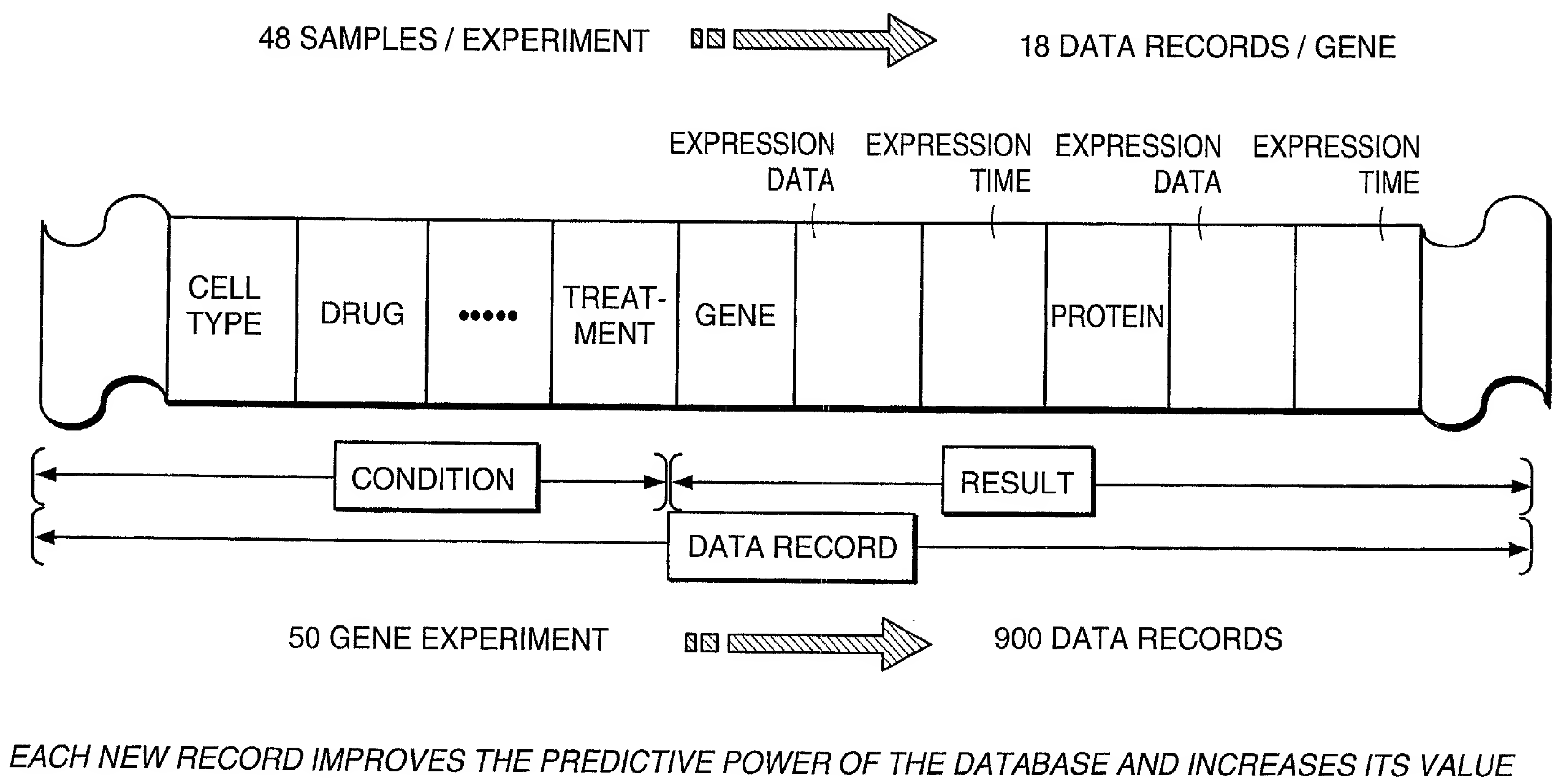

48 SAMPLES / EXPERIMENT
18 DATA RECORDS / GENE
EXPRESSION DATA
EXPRESSION TIME
EXPRESSION DATA
EXPRESSION TIME
CELL TYPE
DRUG
•••••
TREAT-MENT
GENE
PROTEIN
CONDITION
RESULT
DATA RECORD
50 GENE EXPERIMENT
900 DATA RECORDS
EACH NEW RECORD IMPROVES THE PREDICTIVE POWER OF THE DATABASE AND INCREASES ITS VALUE

FIG. 7

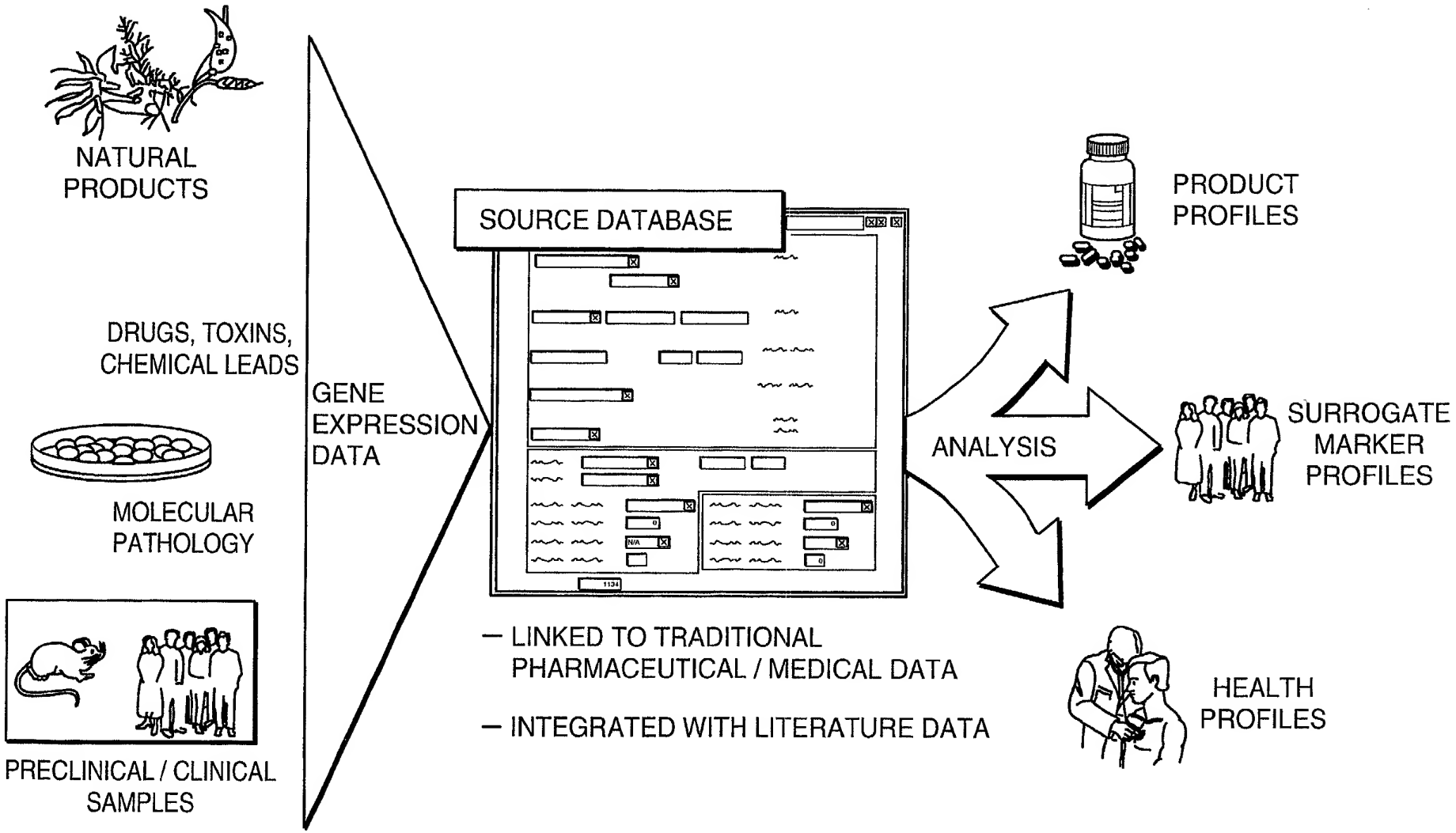

NATURAL PRODUCTS
DRUGS, TOXINS, CHEMICAL LEADS
MOLECULAR PATHOLOGY
PRECLINICAL / CLINICAL SAMPLES
GENE EXPRESSION DATA
SOURCE DATABASE
— LINKED TO TRADITIONAL PHARMACEUTICAL / MEDICAL DATA
— INTEGRATED WITH LITERATURE DATA
ANALYSIS
PRODUCT PROFILES
SURROGATE MARKER PROFILES
HEALTH PROFILES

FIG. 8

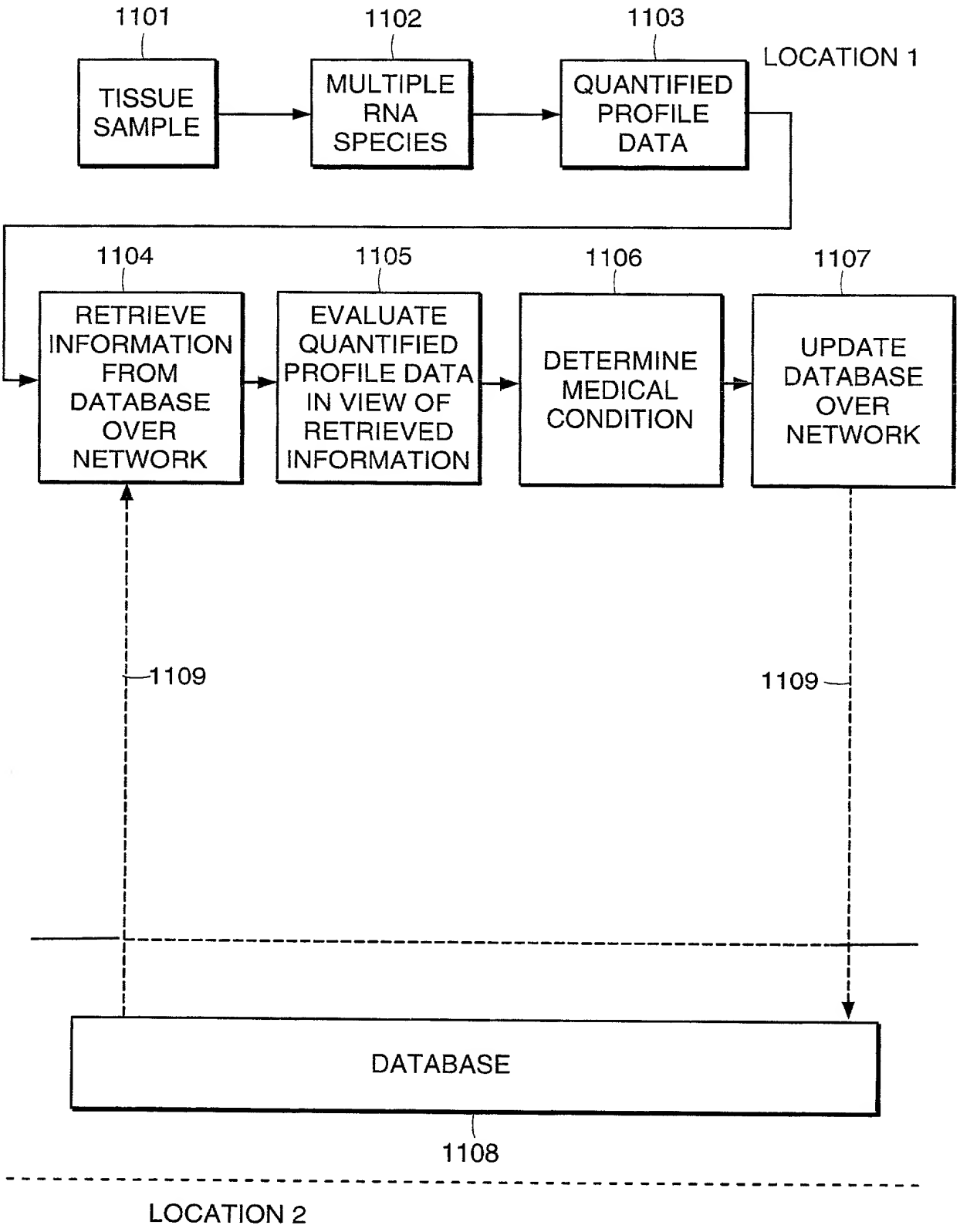
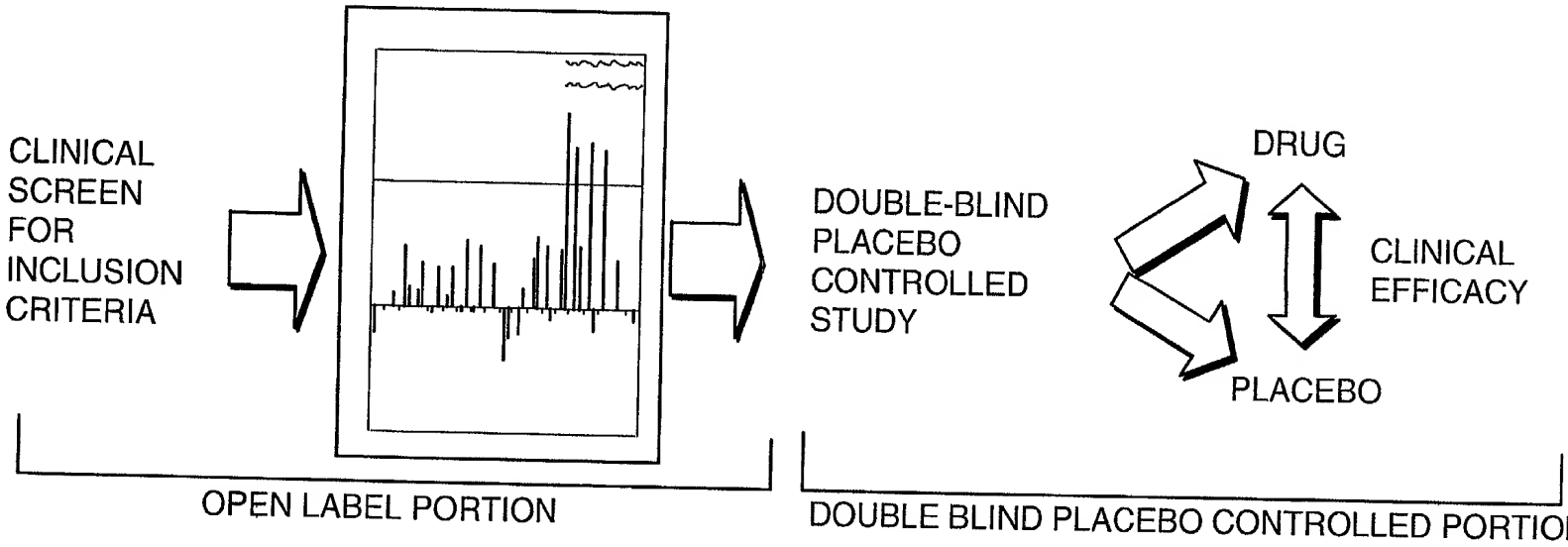

1101
TISSUE SAMPLE
1102
MULTIPLE RNA SPECIES
1103
QUANTIFIED PROFILE DATA
LOCATION 1
1104
RETRIEVE INFORMATION FROM DATABASE OVER NETWORK
1105
EVALUATE QUANTIFIED PROFILE DATA IN VIEW OF RETRIEVED INFORMATION
1106
DETERMINE MEDICAL CONDITION
1107
UPDATE DATABASE OVER NETWORK
1109
1109
DATABASE
1108
LOCATION 2

FIG. 9

PHASE TWO CLINICAL TRIAL DESIGN USING PRECISION PROFILING



- THE TARGET CLINICAL POPULATION CAN BE EVALUATED FOR RESPONSIVENESS TO THERAPY BY FOCUSING ON DRUG RESPONSE GENE PROFILING
- "SIGNAL TO NOISE" CAN BE ENHANCED BY REMOVING NON-RESPONDERS FROM THE SECOND PORTION OF THE STUDY
- DOSE CAN BE OPTIMIZED ON AN INDIVIDUAL BASIS TO MAXIMIZE THE IMPACT ON THERAPEUTIC OUTCOME

FIG. 10a

- CLINICAL RESPONSE/NON-RESPONSE CAN BE CORRELATED WITH DISEASE RESPONSE GENE PROFILING
- CLINICAL EFFICACY CAN BE MEASURED WITH GREATER PRECISION
- FUTURE STUDIES CAN BE PLANNED WITH GREATER CERTAINTY AND STATISTICAL POWER
- COMPARISION WITH CLINICAL DATABASES CAN PROVIDE IMPORTANT INFORMATION REGARDING COMPETITIVE POSITIONING RELATIVE TO EXISTING THERAPIES

FIG. 10b

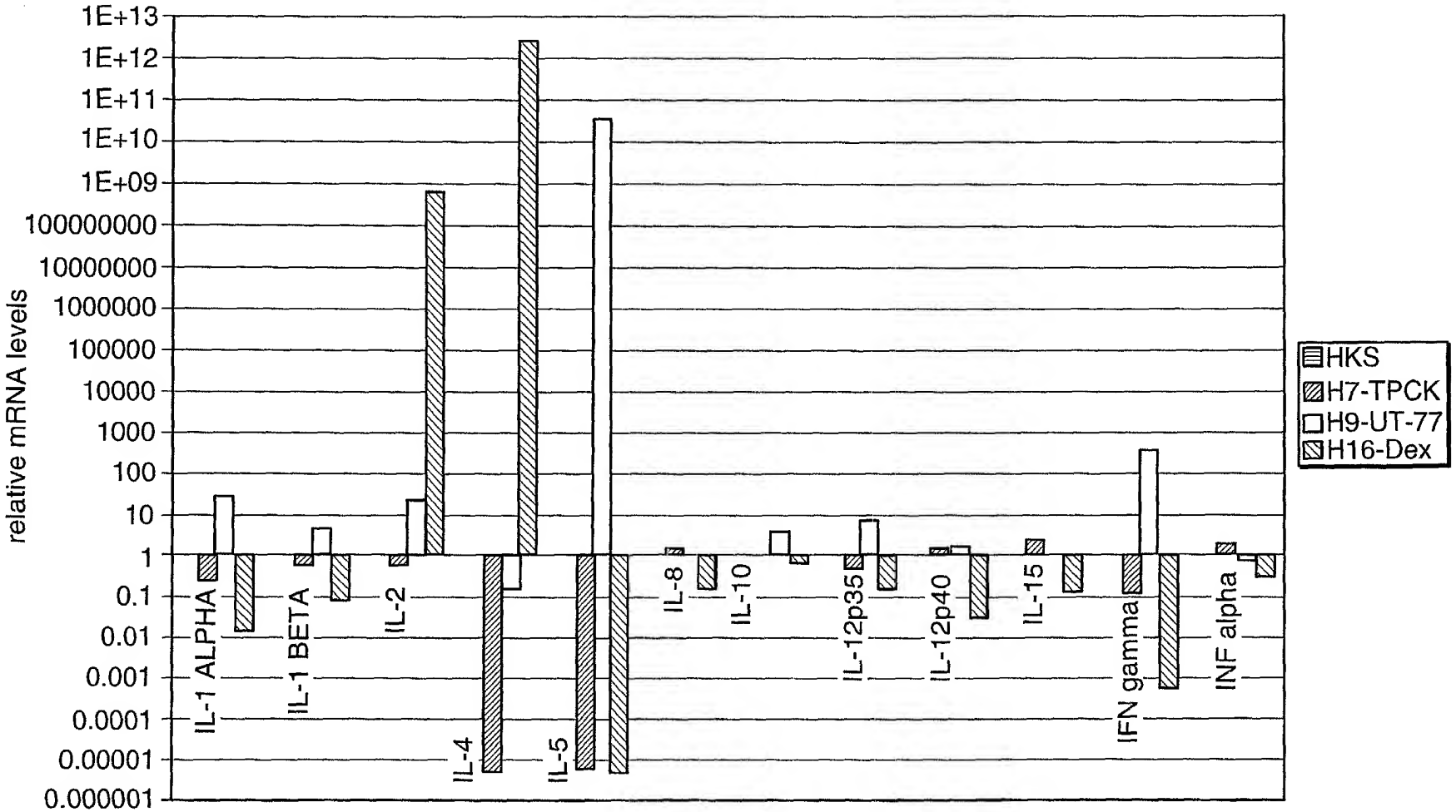


FIG. 11a

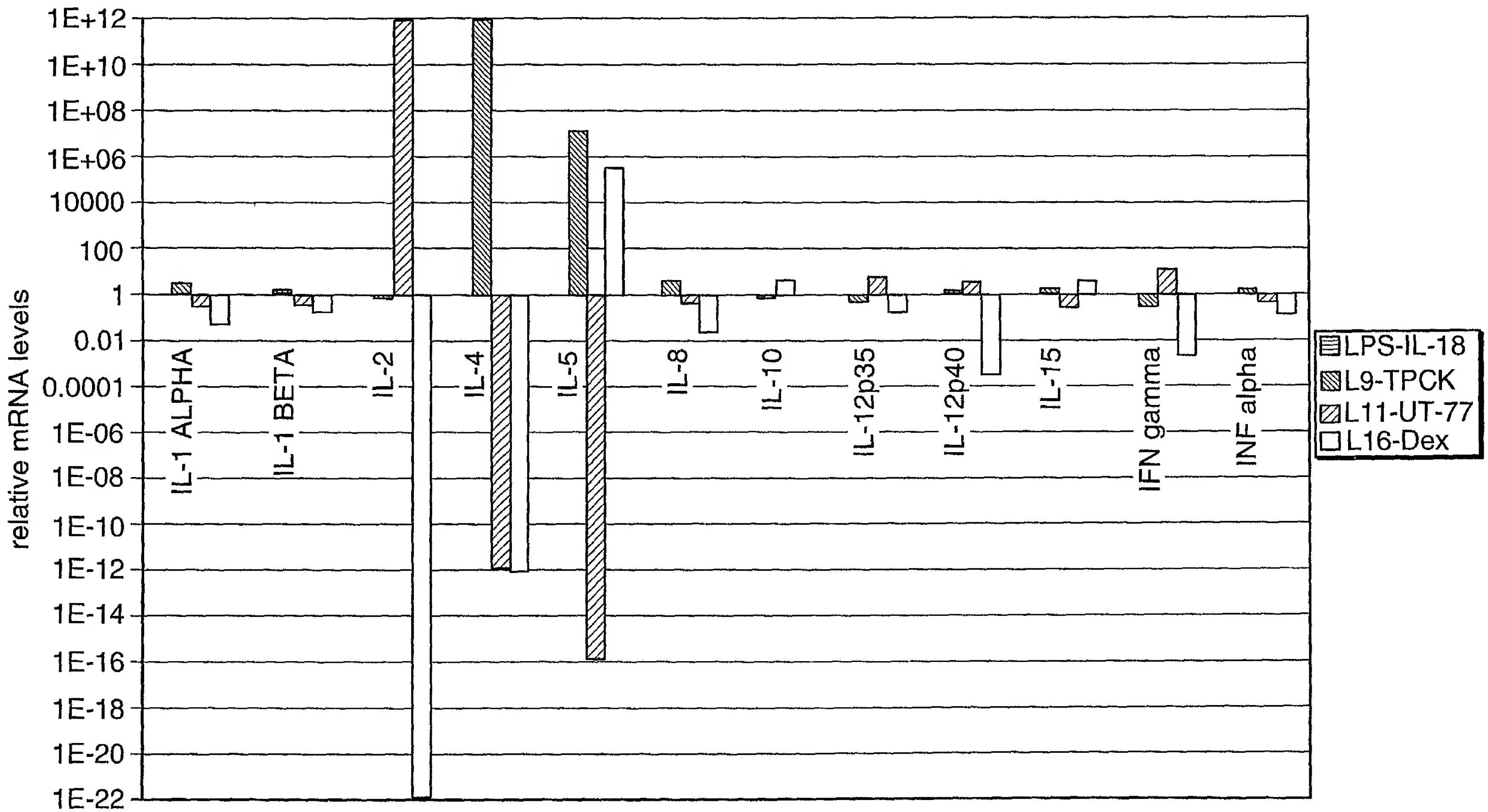


FIG. 11b

COMPARATIVE DRUG PROFILING SHOWS DIFFERENCES AMONG ANTI-INFLAMMATORY DRUGS WITH DIFFERENT MECHANISM OF ACTION

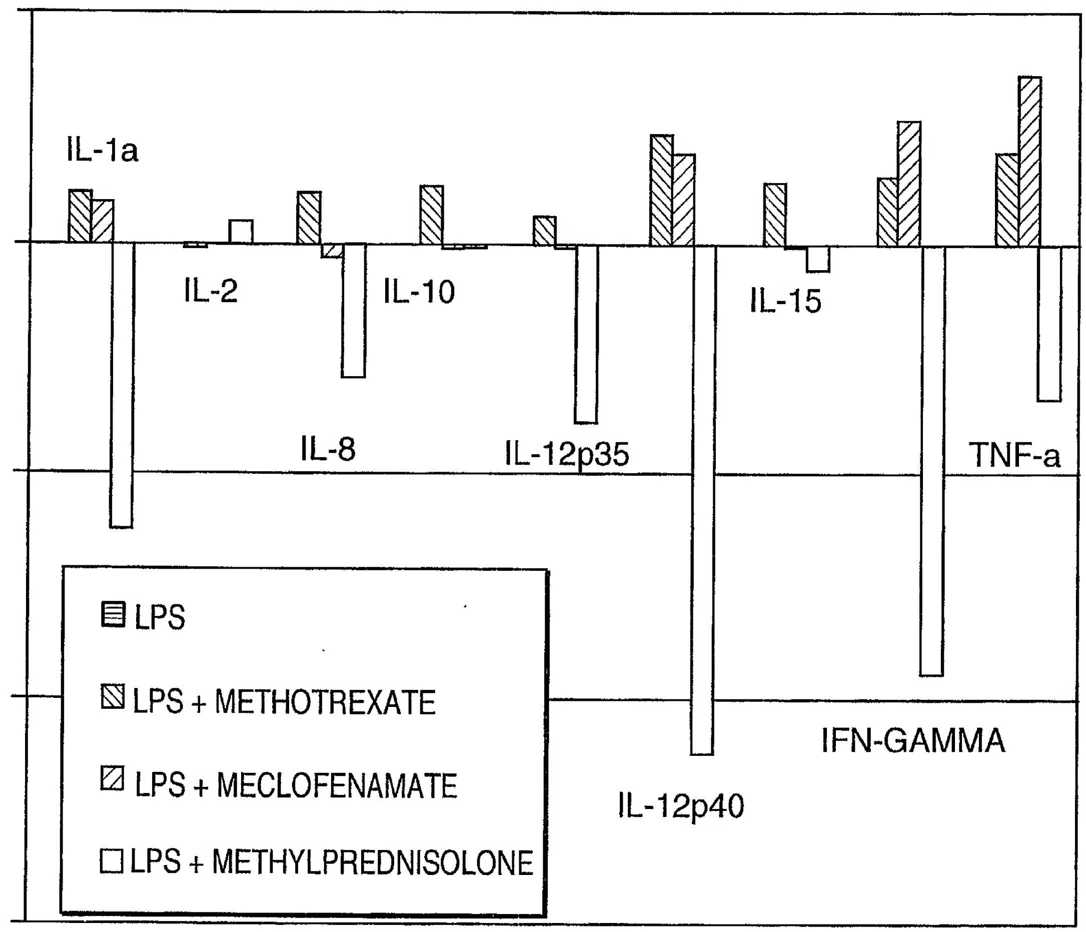


FIG. 12a

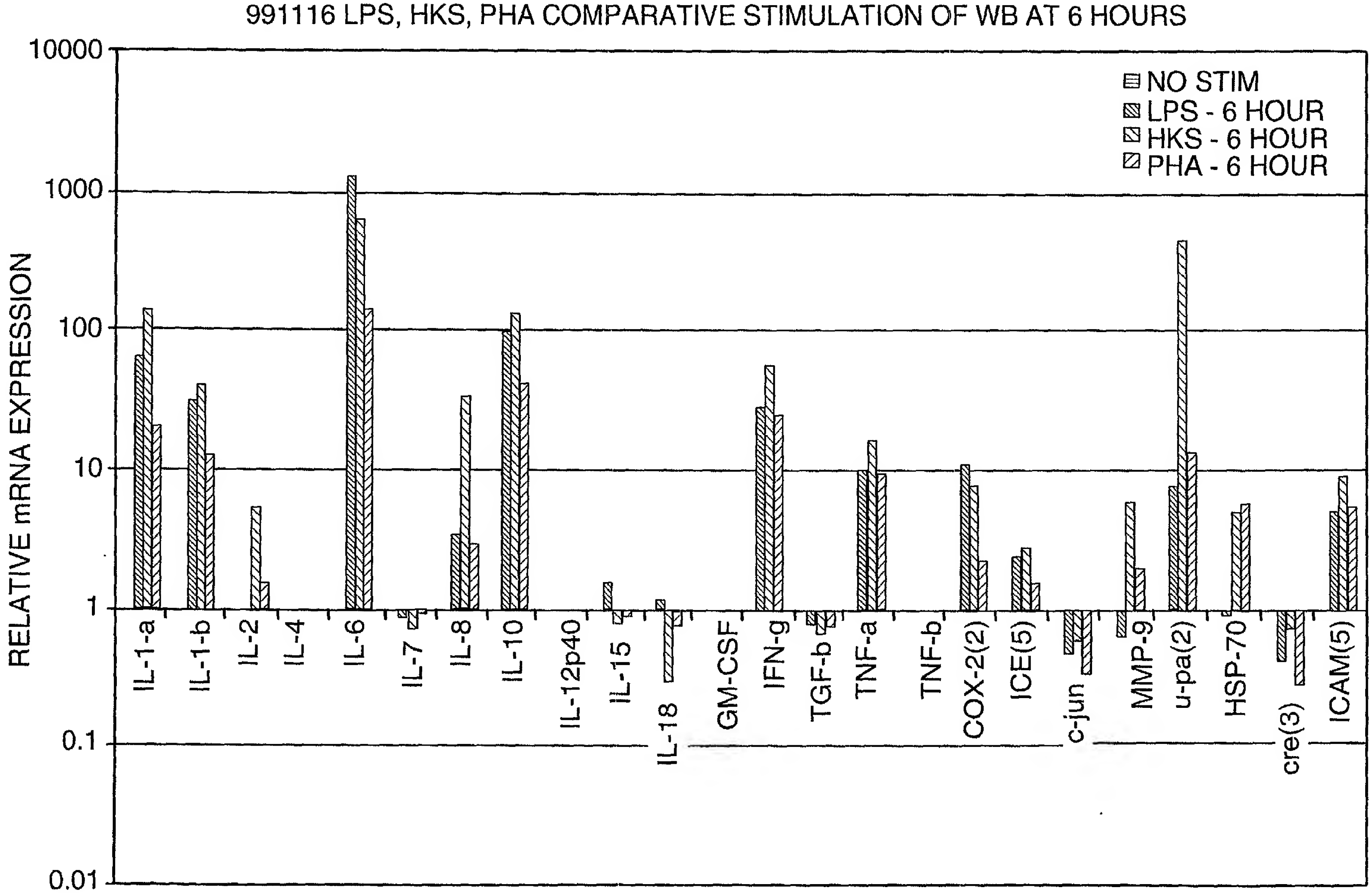


FIG. 13a

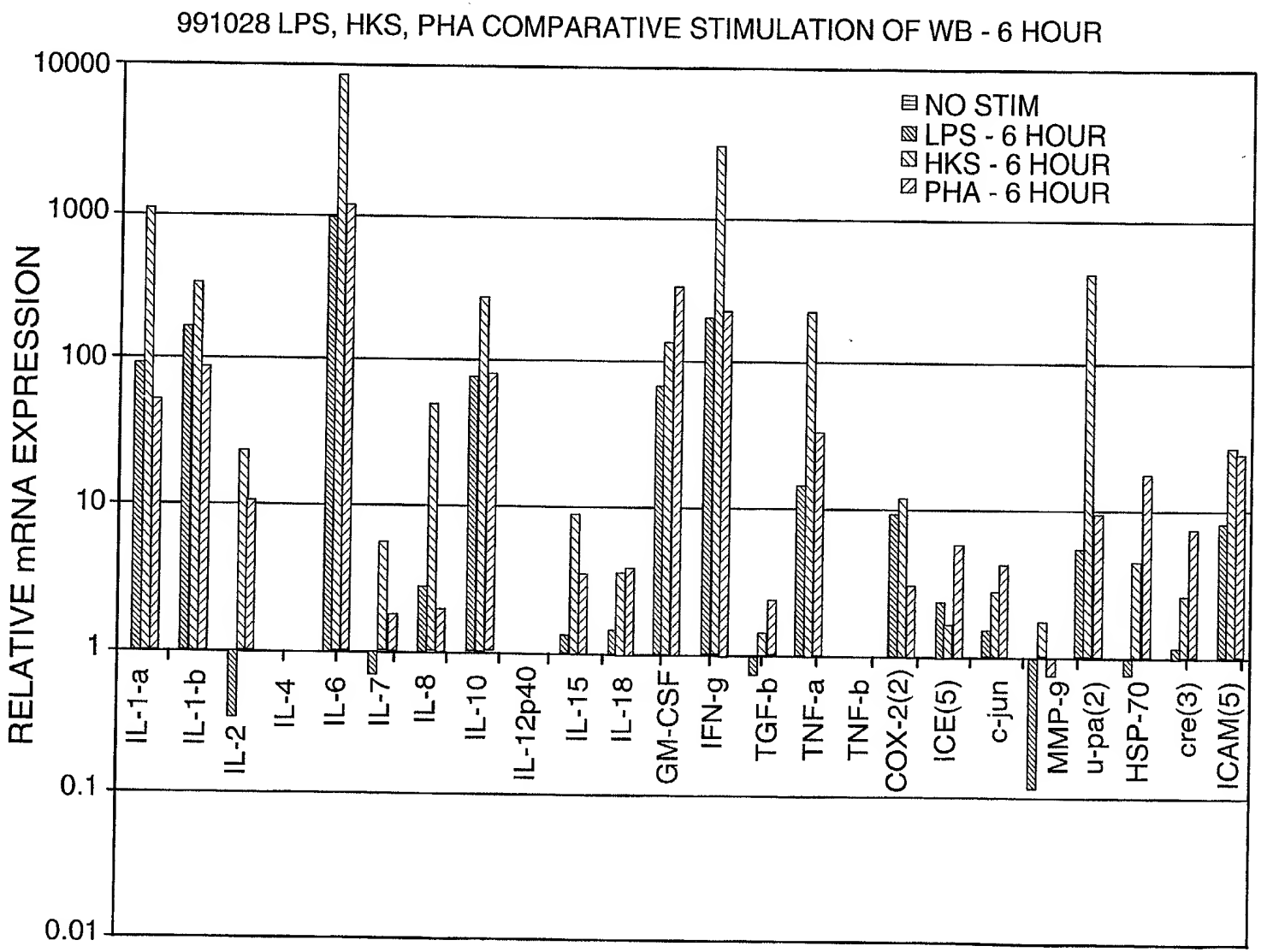

991028 LPS, HKS, PHA COMPARATIVE STIMULATION OF WB - 6 HOUR
RELATIVE mRNA EXPRESSION
10000
1000
100
10
1
0.1
0.01
NO STIM
LPS - 6 HOUR
HKS - 6 HOUR
PHA - 6 HOUR
IL-1-a
IL-1-b
IL-2
IL-4
IL-6
IL-7
IL-8
IL-10
IL-12p40
IL-15
IL-18
GM-CSF
IFN-g
TGF-b
TNF-a
TNF-b
COX-2(2)
ICE(5)
c-jun
MMP-9
u-pa(2)
HSP-70
cre(3)
ICAM(5)

FIG. 13b

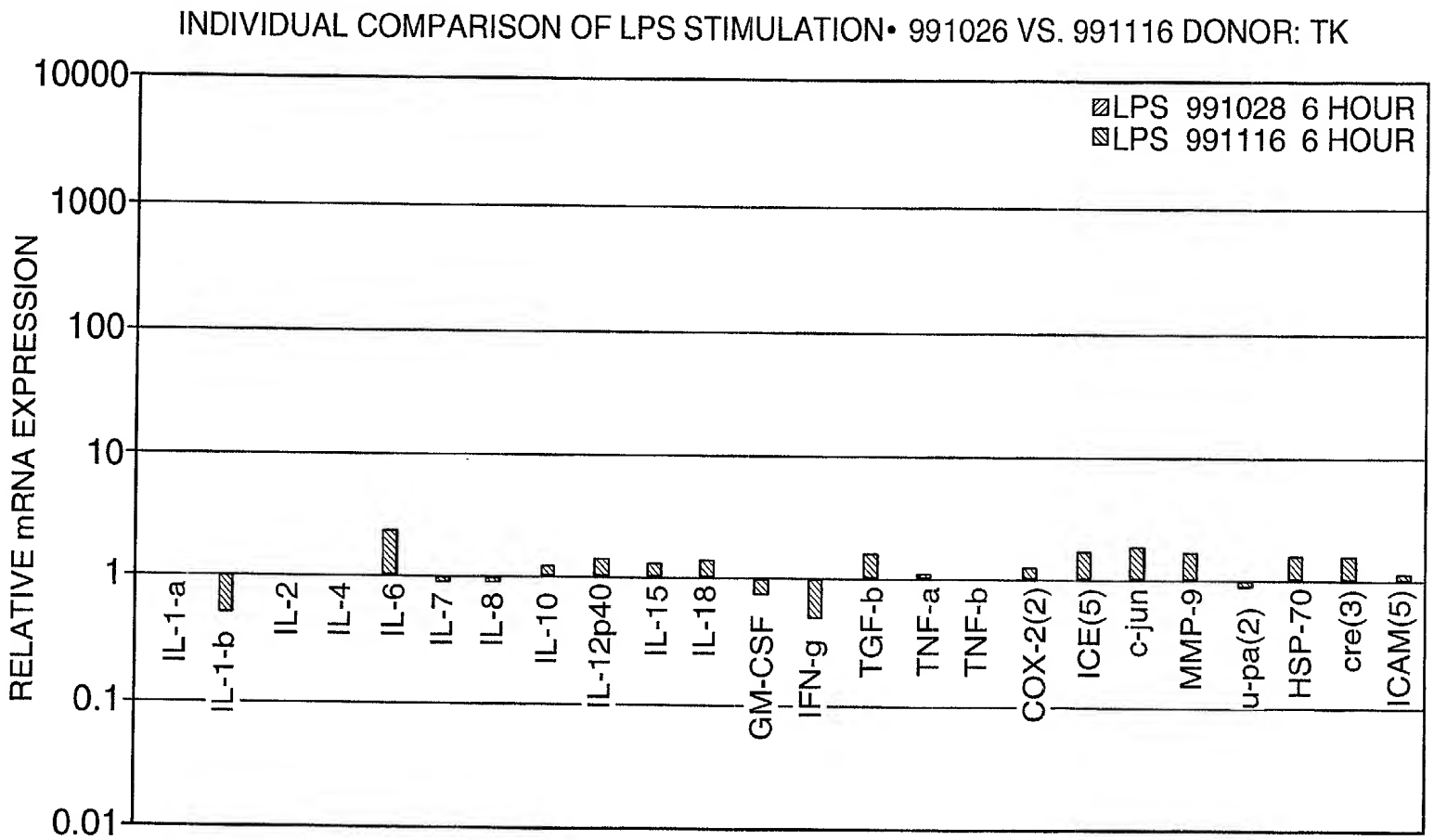


FIG. 13c

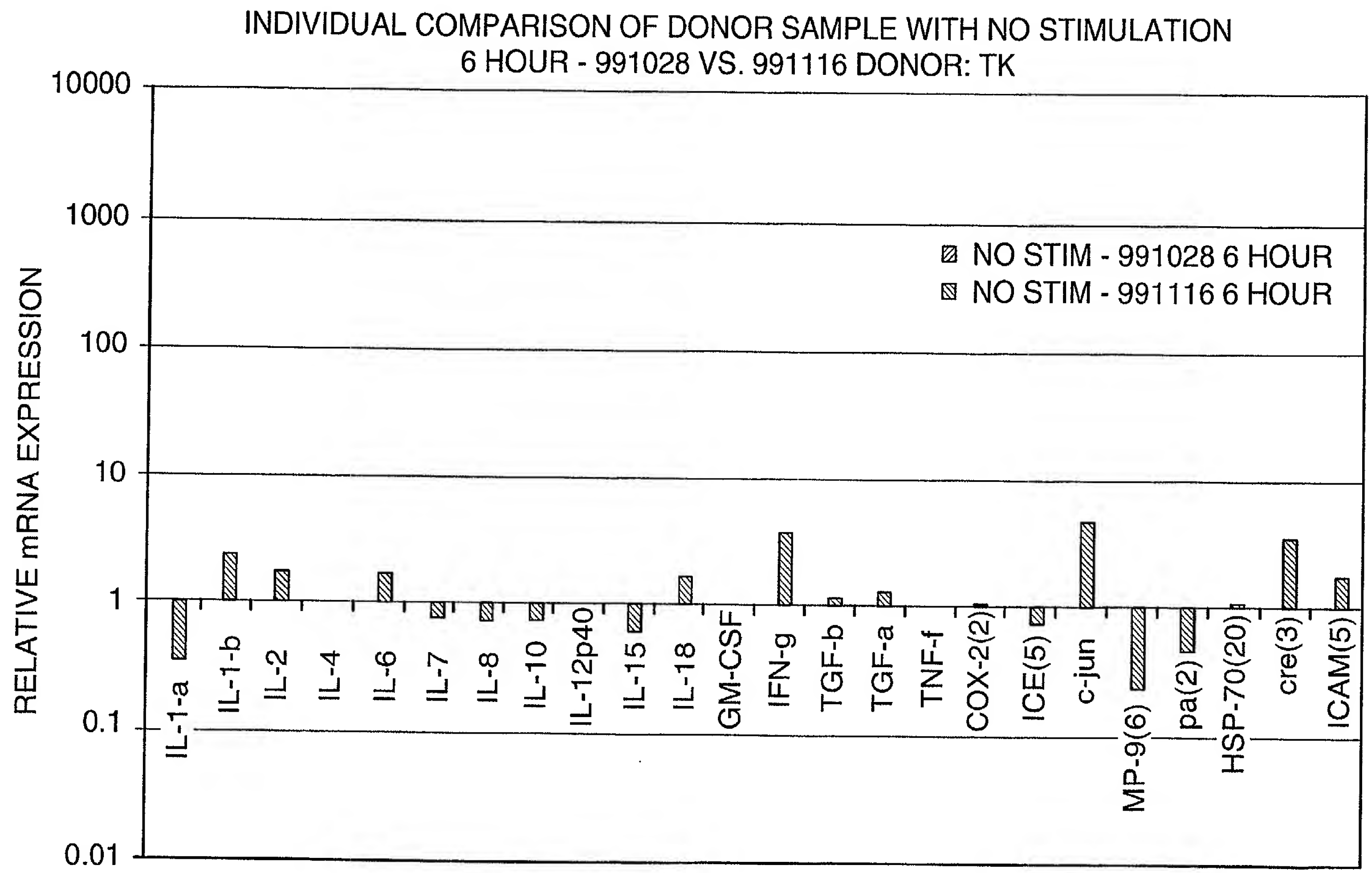

INDIVIDUAL COMPARISON OF DONOR SAMPLE WITH NO STIMULATION
6 HOUR - 991028 VS. 991116 DONOR: TK
RELATIVE mRNA EXPRESSION
10000
1000
100
10
1
0.1
0.01
NO STIM - 991028 6 HOUR
NO STIM - 991116 6 HOUR
IL-1-a
IL-1-b
IL-2
IL-4
IL-6
IL-7
IL-8
IL-10
IL-12p40
IL-15
IL-18
GM-CSF
IFN-g
TGF-b
TGF-a
TNF-f
COX-2(2)
ICE(5)
c-jun
MP-9(6)
pa(2)
HSP-70(20)
cre(3)
ICAM(5)

FIG. 13d

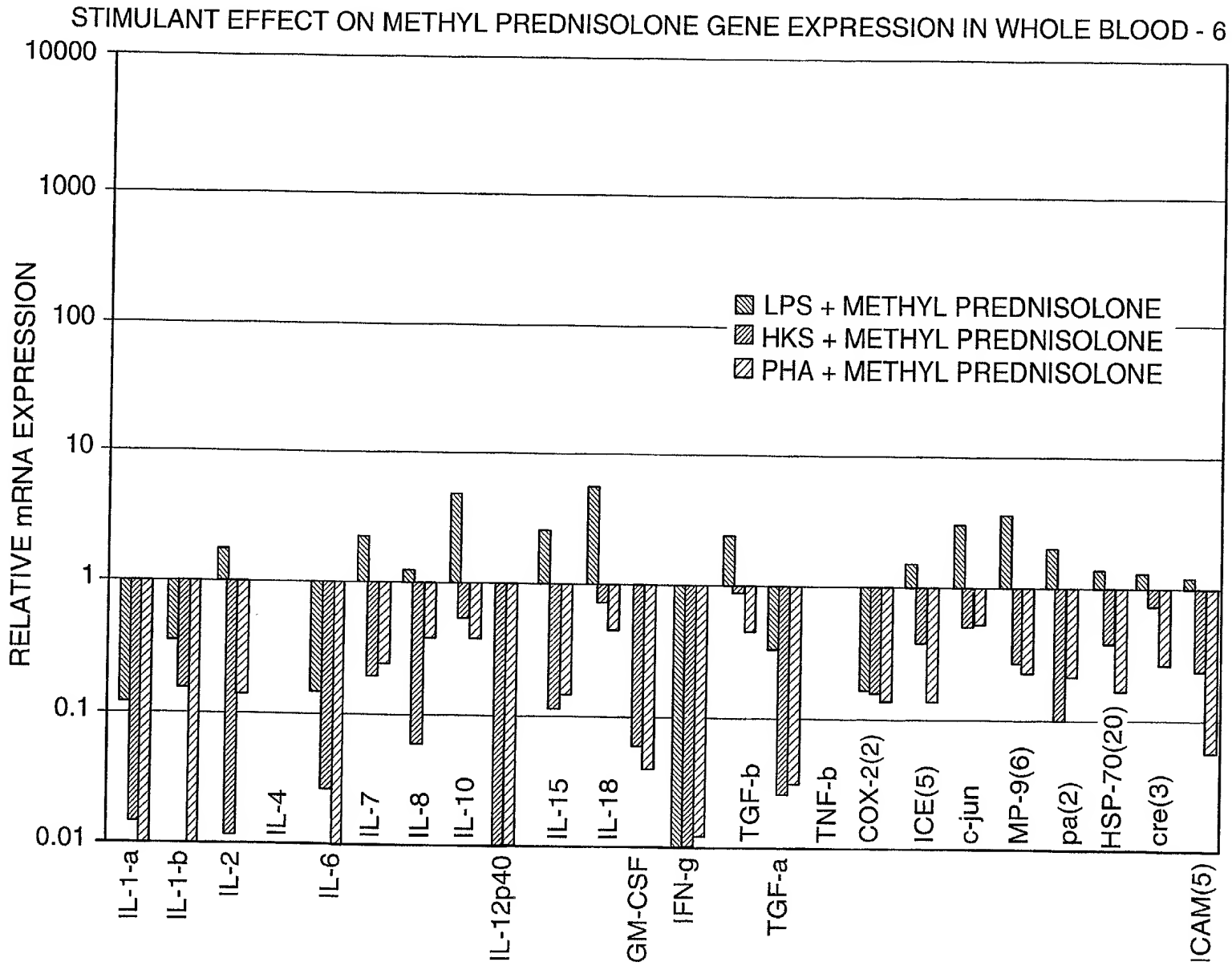

STIMULANT EFFECT ON METHYL PREDNISOLONE GENE EXPRESSION IN WHOLE BLOOD - 6 HOUR
RELATIVE mRNA EXPRESSION
10000
1000
100
10
1
0.1
0.01
LPS + METHYL PREDNISOLONE
HKS + METHYL PREDNISOLONE
PHA + METHYL PREDNISOLONE
IL-1-a
IL-1-b
IL-2
IL-4
IL-6
IL-7
IL-8
IL-10
IL-12p40
IL-15
IL-18
GM-CSF
IFN-g
TGF-b
TGF-a
TNF-b
COX-2(2)
ICE(5)
c-jun
MP-9(6)
pa(2)
HSP-70(20)
cre(3)
ICAM(5)

FIG. 14

COMPARISON OF IN VITRO AND IN VIVO GENE EXPRESSION IN RESPONSE TO CORTICOSTEROID TREATMENT

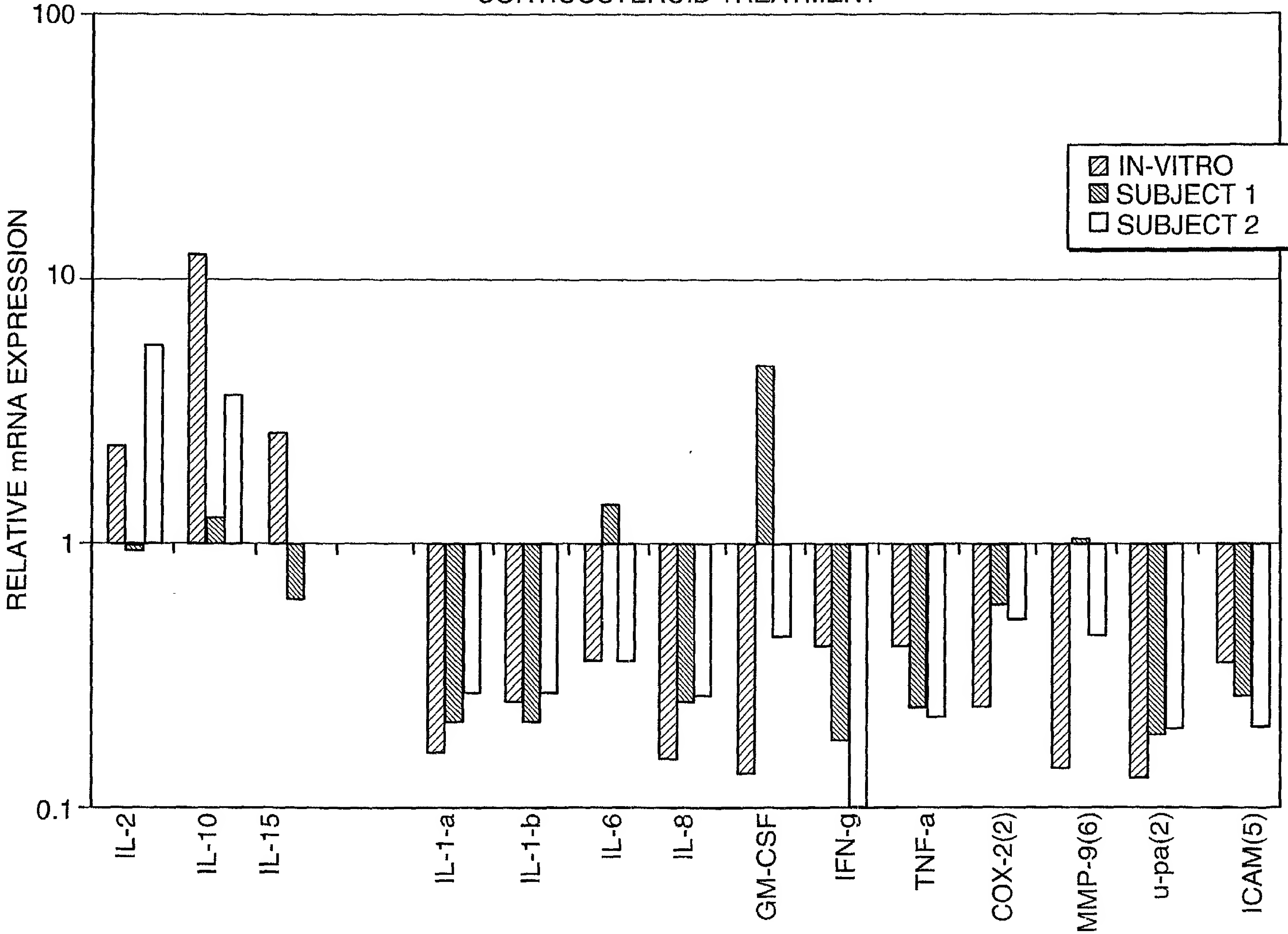


FIG. 15

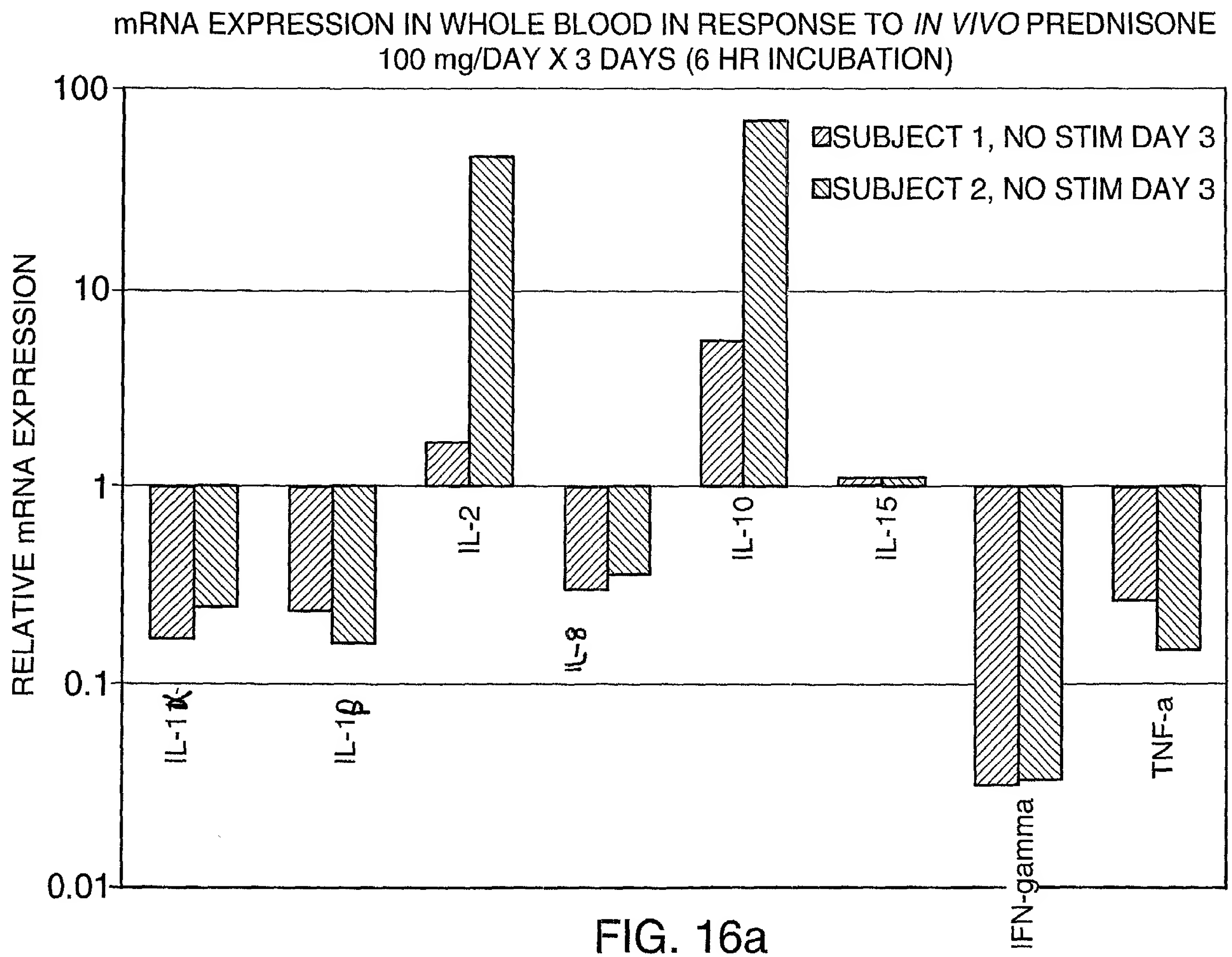


FIG. 16a

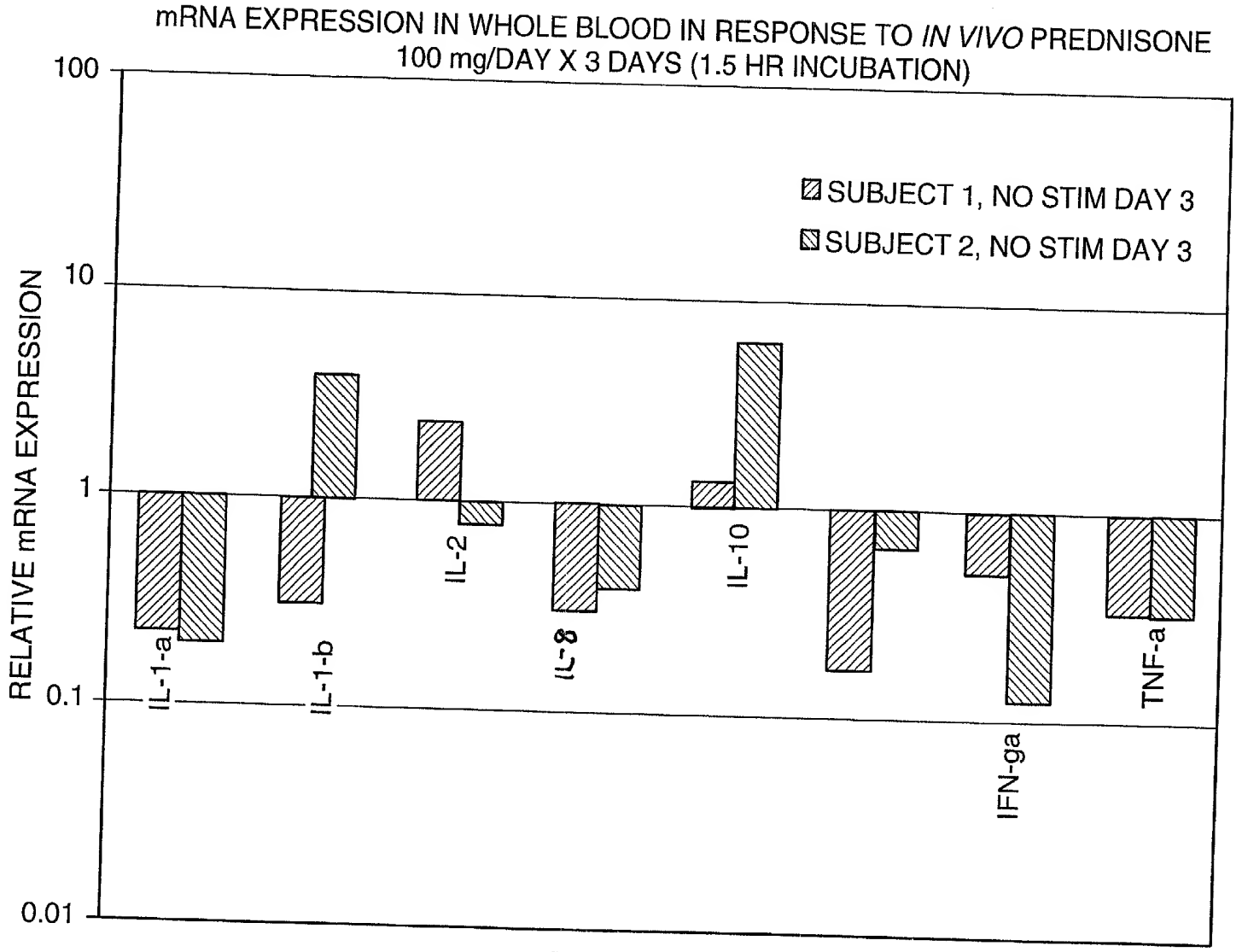

mRNA EXPRESSION IN WHOLE BLOOD IN RESPONSE TO *IN VIVO* PREDNISONE
100 mg/DAY X 3 DAYS (1.5 HR INCUBATION)
RELATIVE mRNA EXPRESSION
100
10
1
0.1
0.01
SUBJECT 1, NO STIM DAY 3
SUBJECT 2, NO STIM DAY 3
IL-1-a
IL-1-b
IL-2
IL-8
IL-10
IFN-ga
TNF-a

FIG. 16b

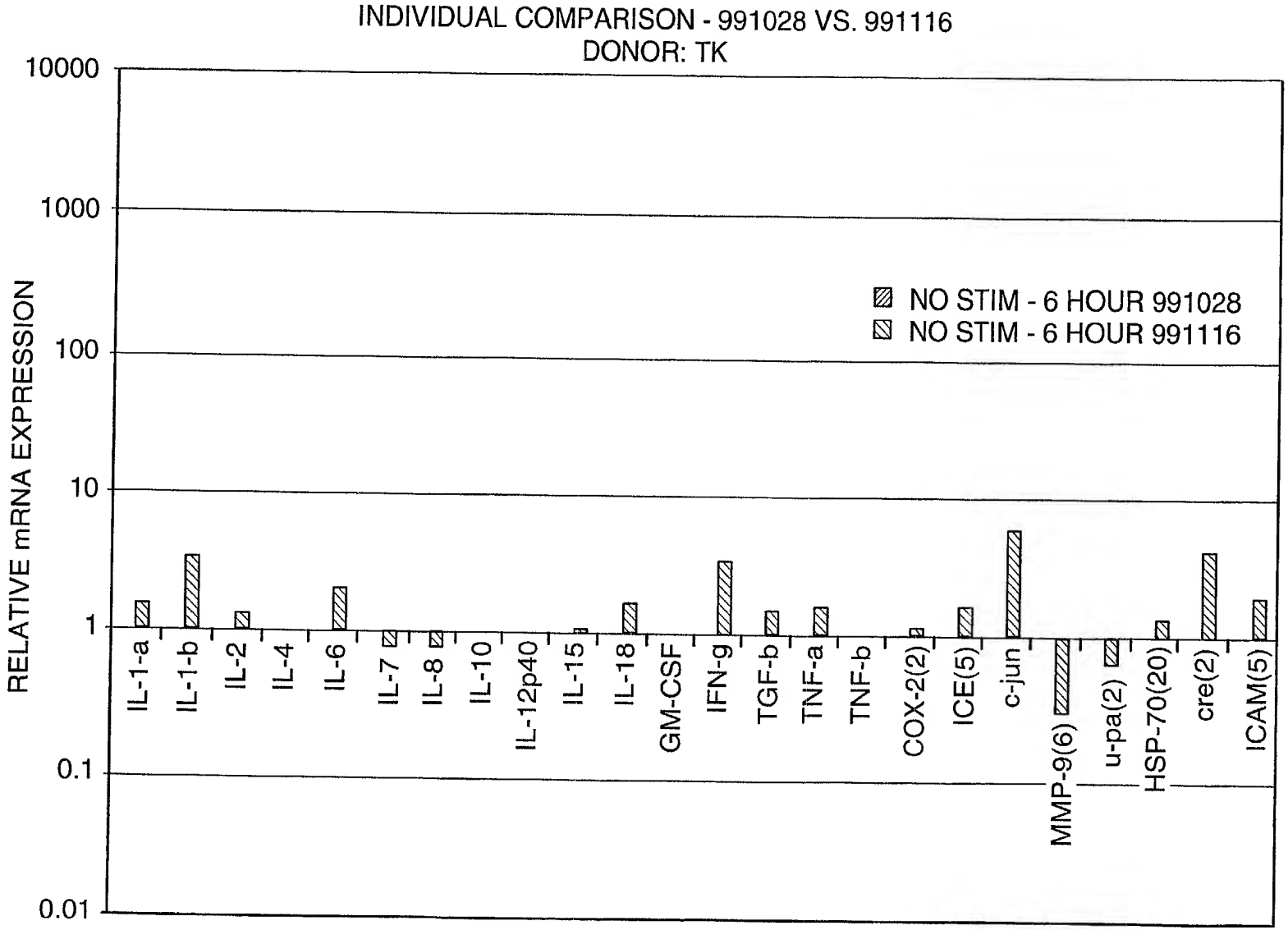

INDIVIDUAL COMPARISON - 991028 VS. 991116
DONOR: TK
RELATIVE mRNA EXPRESSION
10000
1000
100
10
1
0.1
0.01
NO STIM - 6 HOUR 991028
NO STIM - 6 HOUR 991116
IL-1-a
IL-1-b
IL-2
IL-4
IL-6
IL-7
IL-8
IL-10
IL-12p40
IL-15
IL-18
GM-CSF
IFN-g
TGF-b
TNF-a
TNF-b
COX-2(2)
ICE(5)
c-jun
MMP-9(6)
u-pa(2)
HSP-70(20)
cre(2)
ICAM(5)

FIG. 17

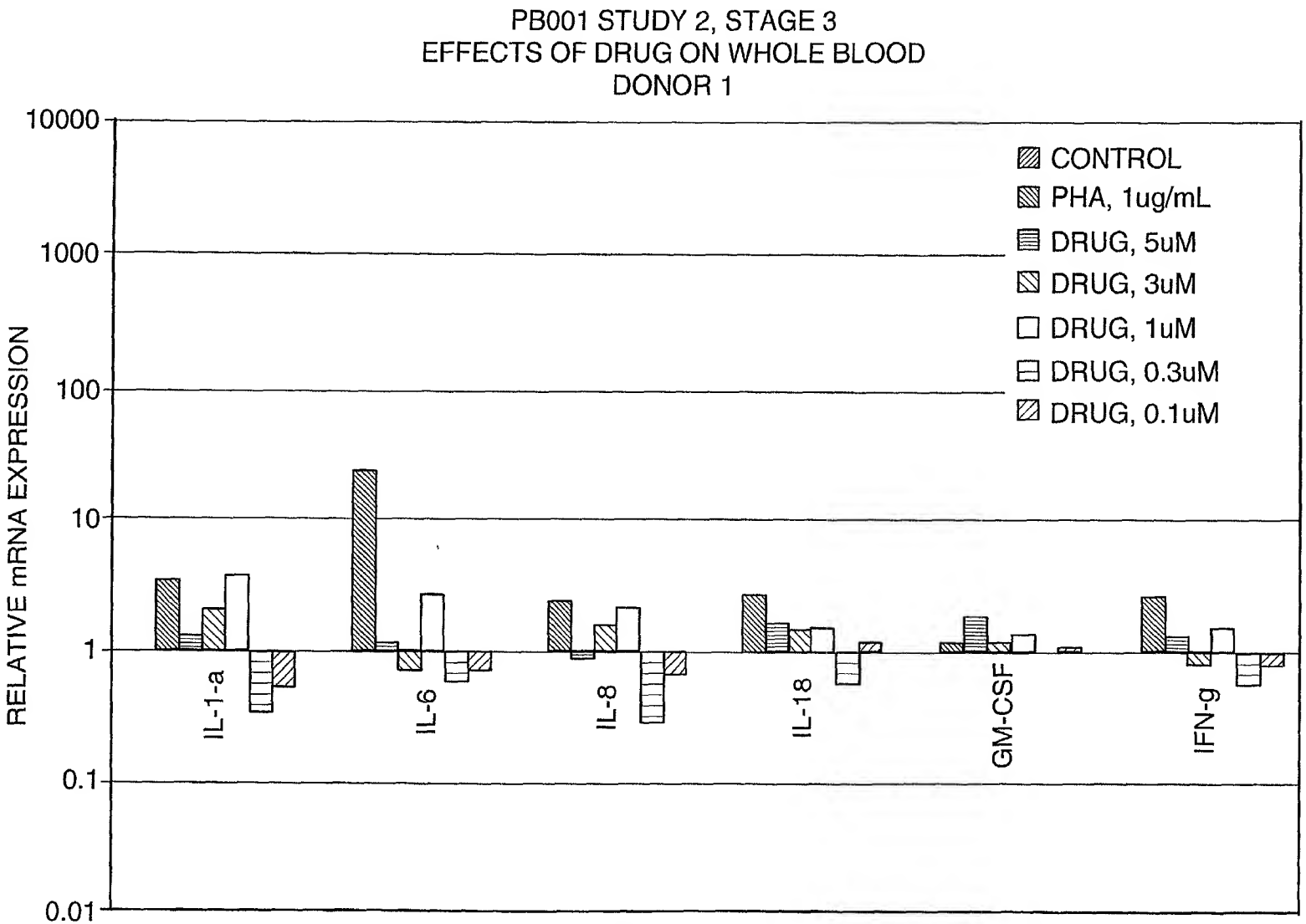

PB001 STUDY 2, STAGE 3
EFFECTS OF DRUG ON WHOLE BLOOD
DONOR 1
RELATIVE mRNA EXPRESSION
10000
1000
100
10
1
0.1
0.01
CONTROL
PHA, 1ug/mL
DRUG, 5uM
DRUG, 3uM
DRUG, 1uM
DRUG, 0.3uM
DRUG, 0.1uM
IL-1-a
IL-6
IL-8
IL-18
GM-CSF
IFN-g

FIG. 18a

PB001 STUDY 2, STAGE 3
EFFECTS OF DRUG ON WHOLE BLOOD
DONOR 2

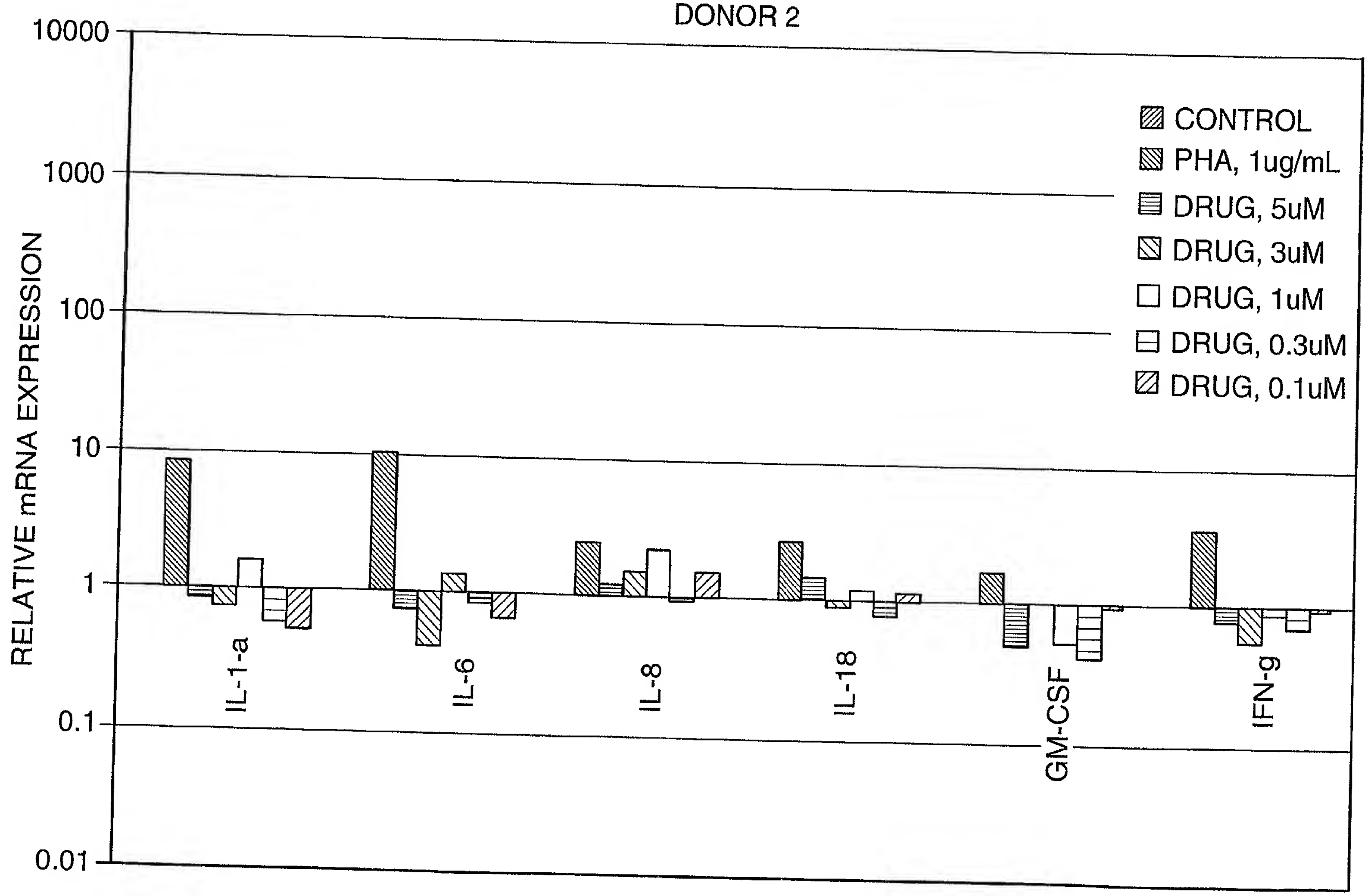


FIG. 18b

PB001 STUDY 2, STAGE 3
EFFECTS OF DRUG ON WHOLE BLOOD
DONOR 3

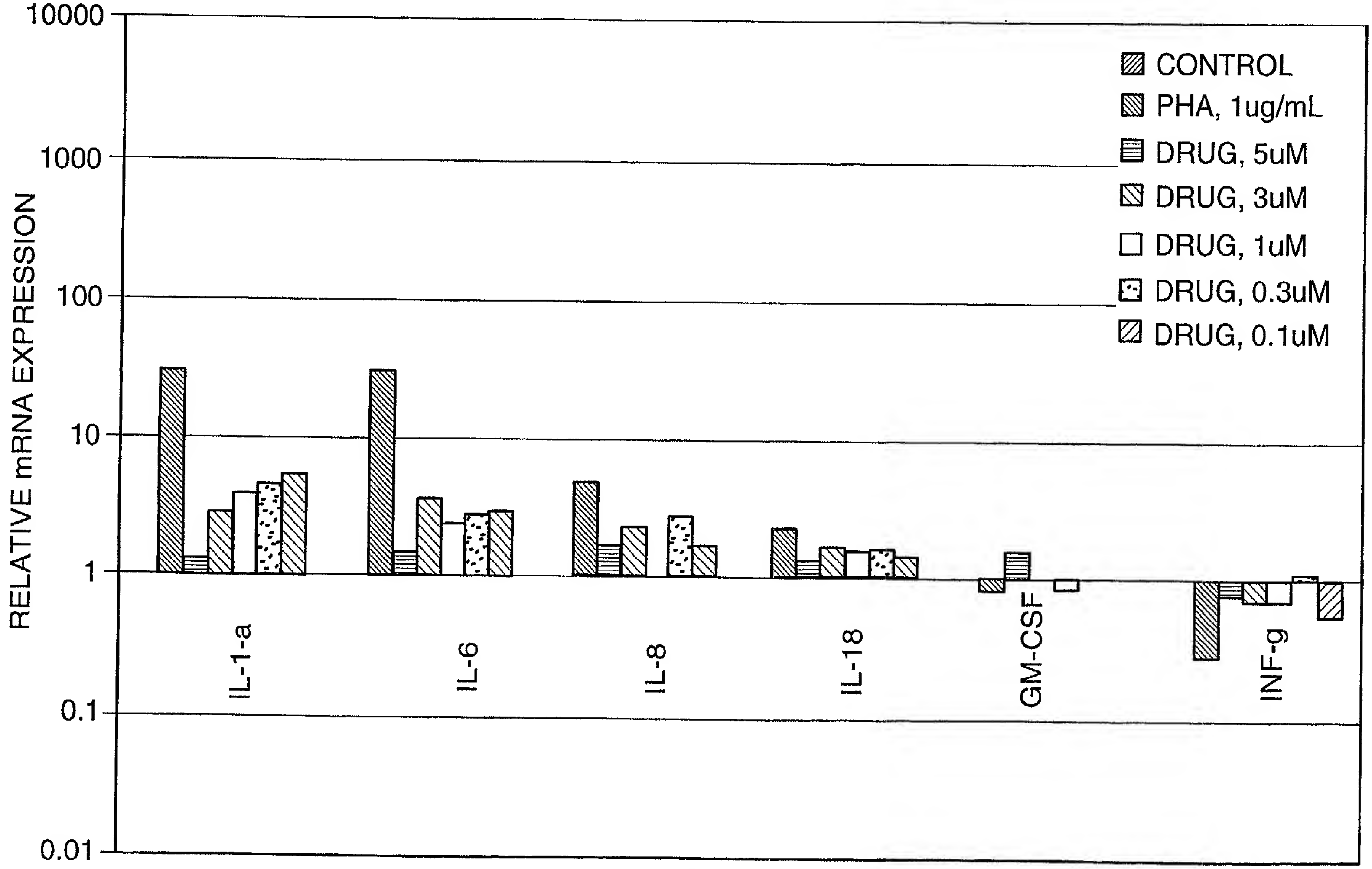


FIG. 18c

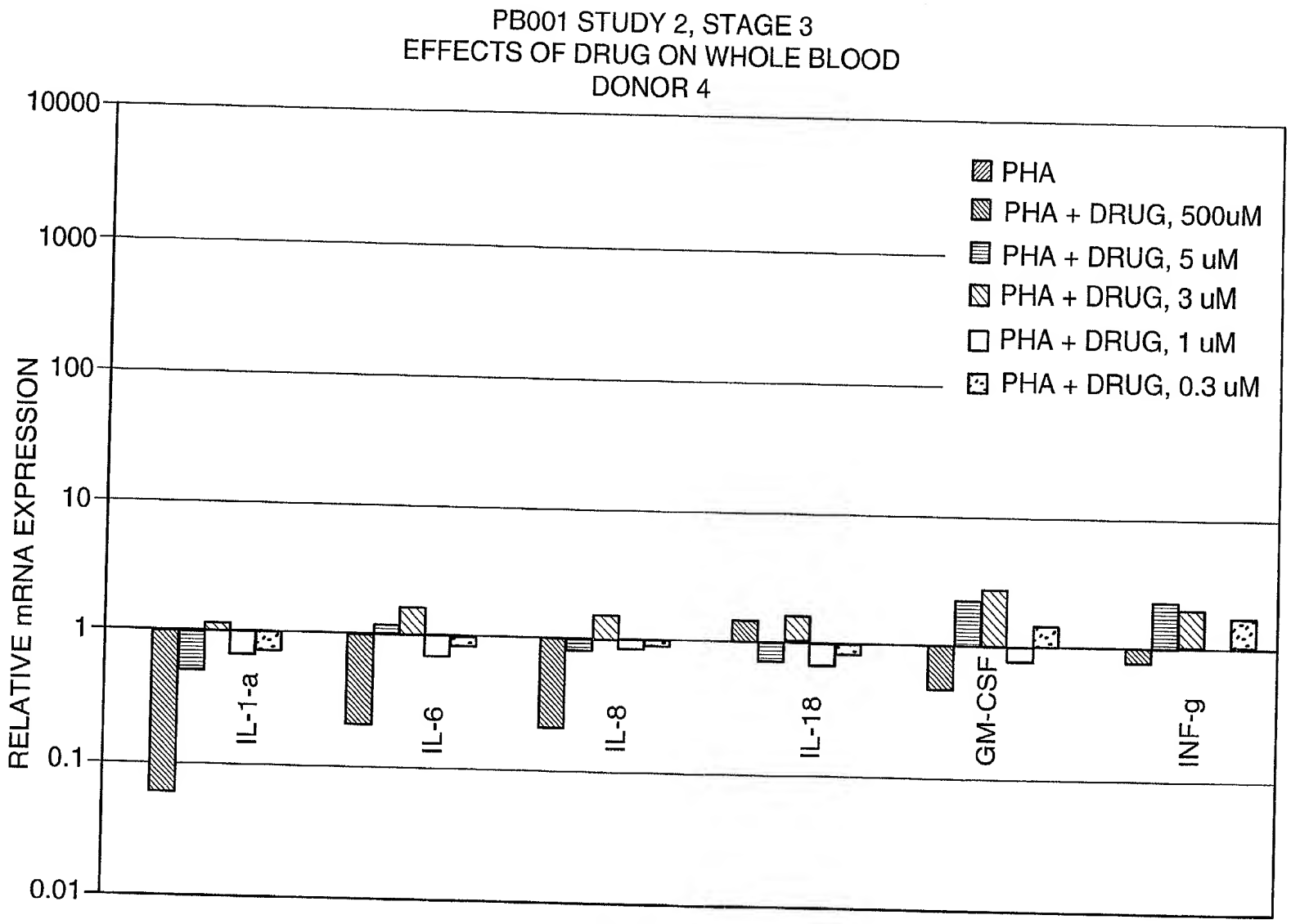


FIG. 18d

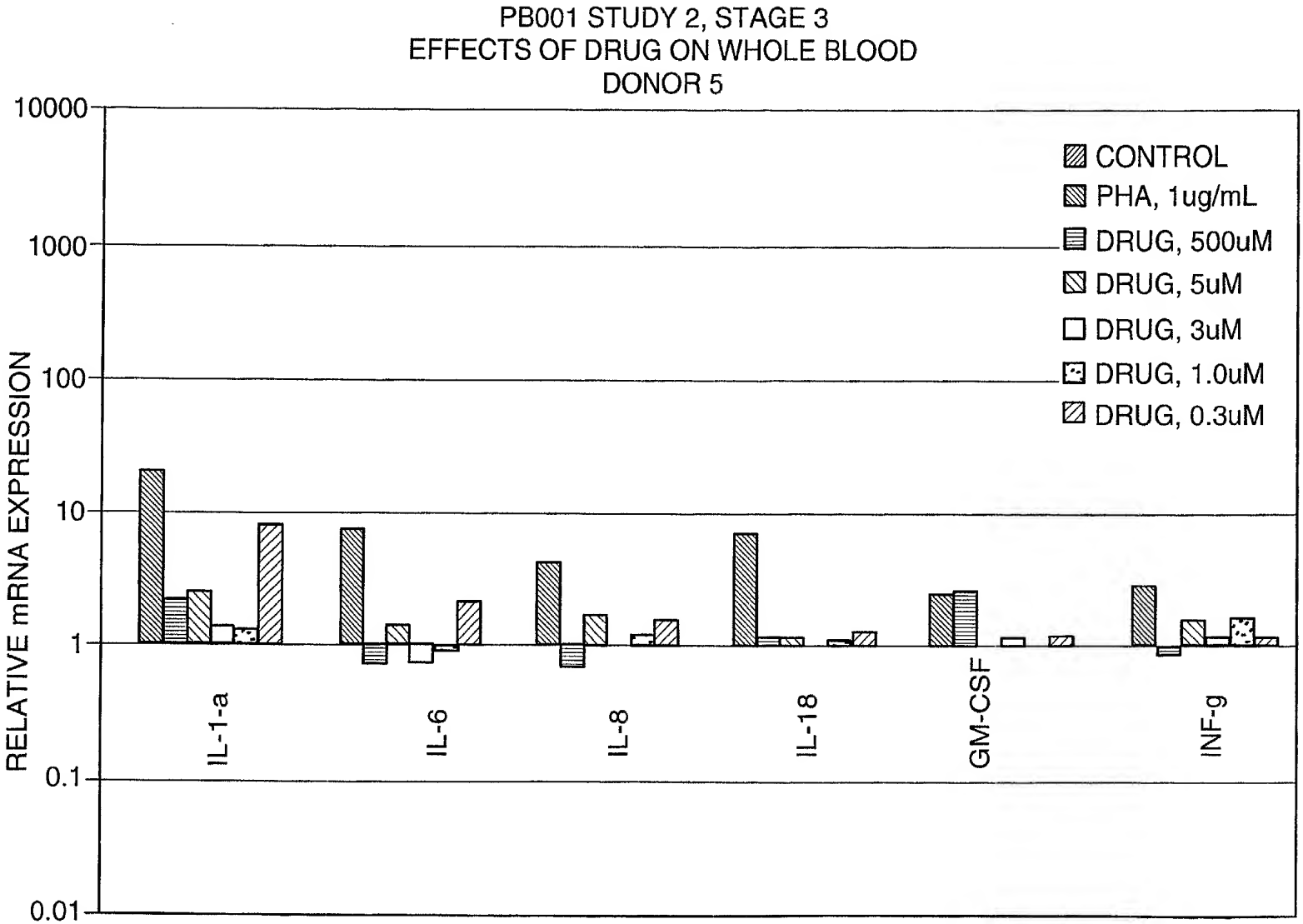


FIG. 18e

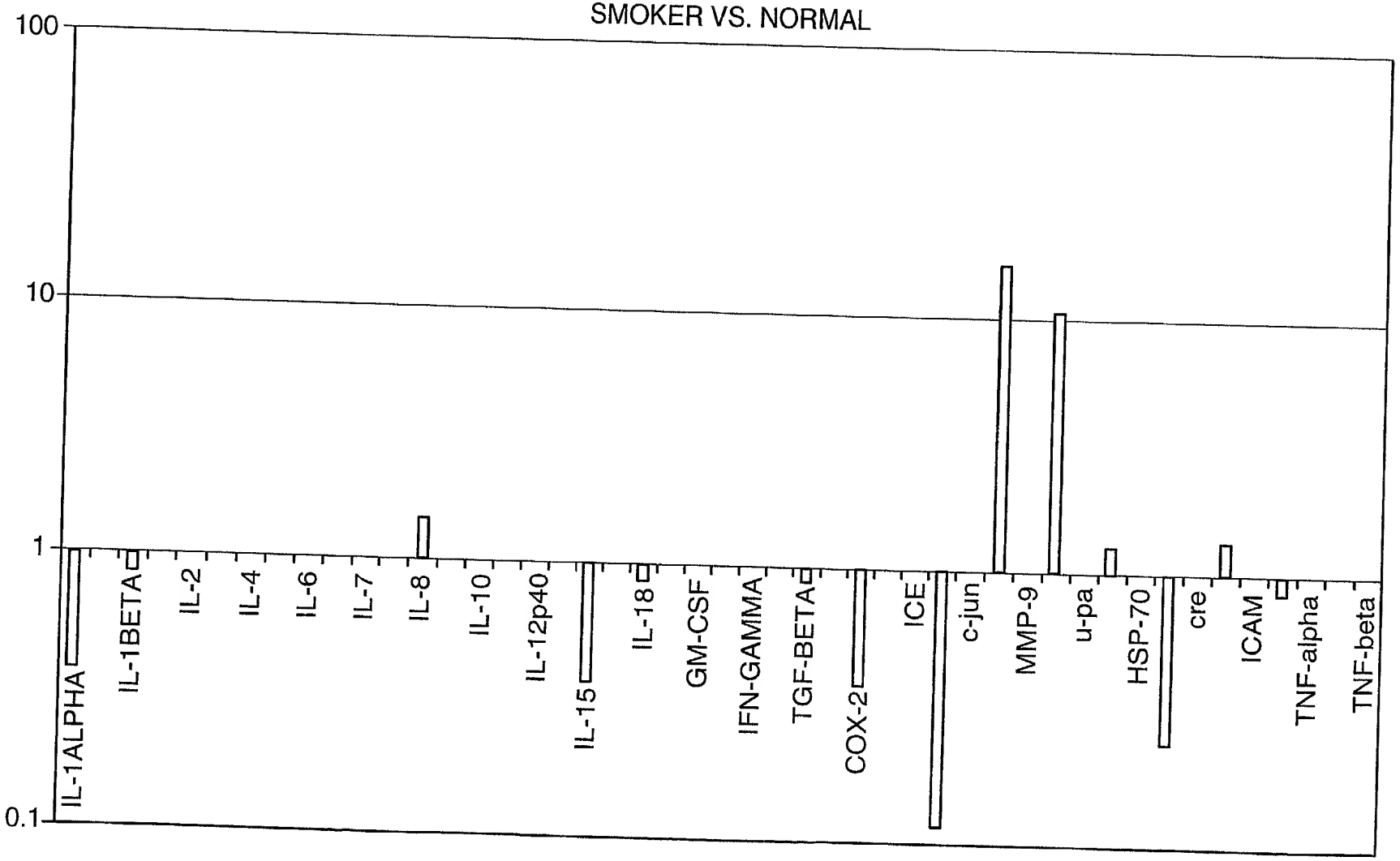

SMOKER VS. NORMAL
100
10
1
0.1
IL-1ALPHA
IL-1BETA
IL-2
IL-4
IL-6
IL-7
IL-8
IL-10
IL-12p40
IL-15
IL-18
GM-CSF
IFN-GAMMA
TGF-BETA
COX-2
ICE
c-jun
MMP-9
u-pa
HSP-70
cre
ICAM
TNF-alpha
TNF-beta

FIG. 19a

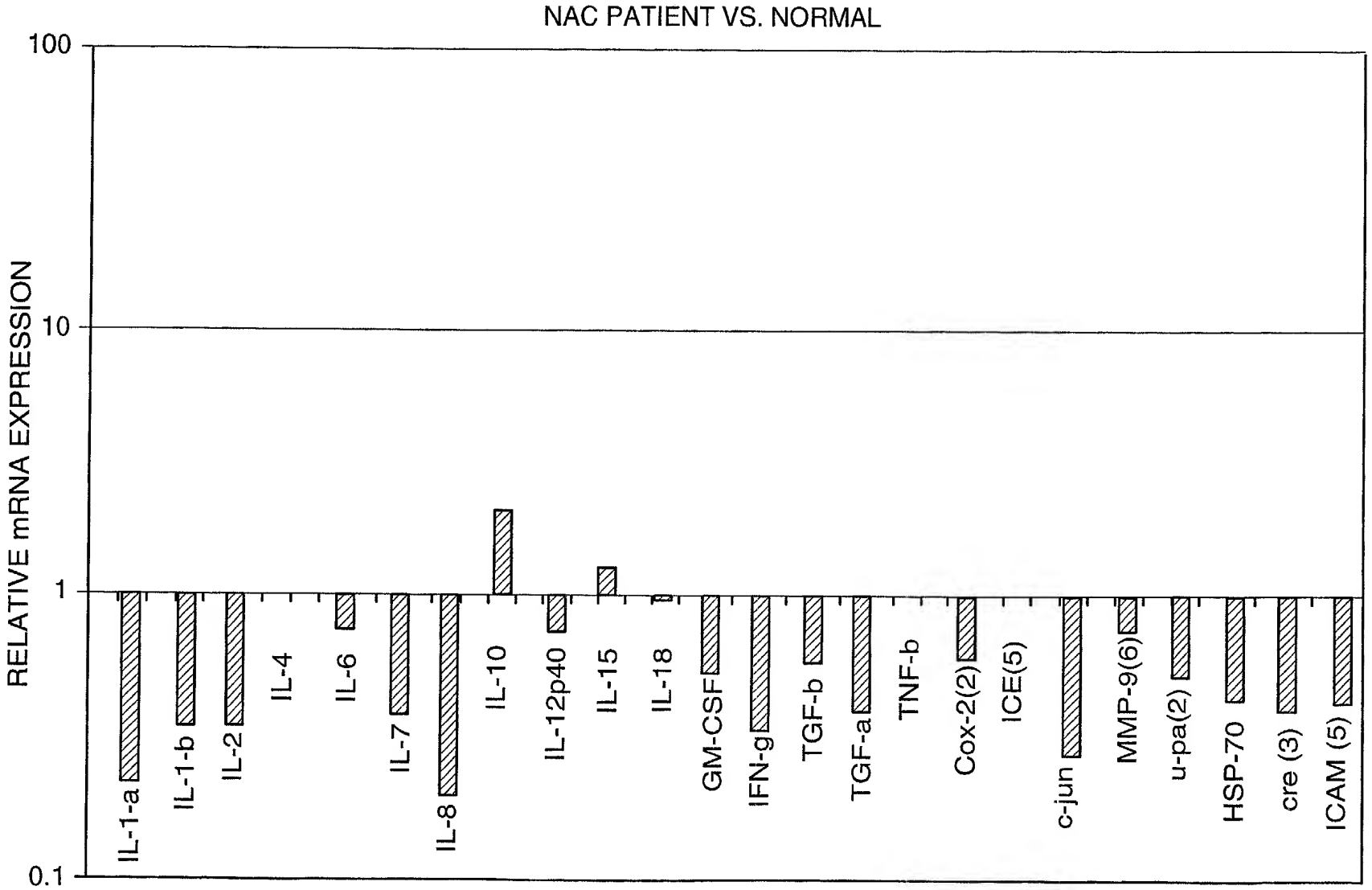

NAC PATIENT VS. NORMAL
RELATIVE mRNA EXPRESSION
100
10
1
0.1
IL-1-a
IL-1-b
IL-2
IL-4
IL-6
IL-7
IL-8
IL-10
IL-12p40
IL-15
IL-18
GM-CSF
IFN-g
TGF-b
TGF-a
TNF-b
Cox-2(2)
ICE(5)
c-jun
MMP-9(6)
u-pa(2)
HSP-70
cre (3)
ICAM (5)

FIG. 19b

EXPRESSION OF GST-P GENE IN INDIVIDUAL RATS FOLLOWING A TOXIC DOSE OF ACETAMINOPHEN

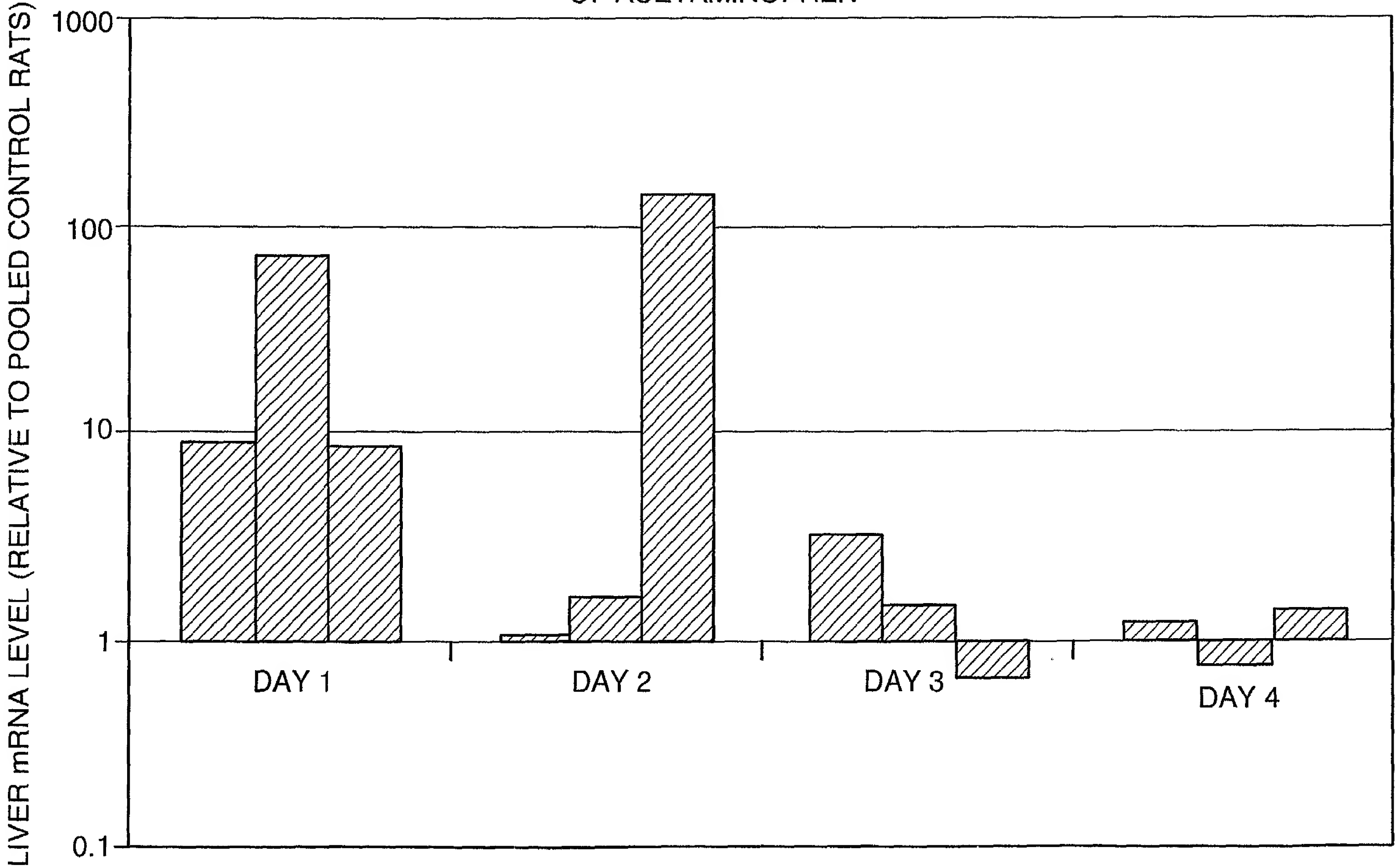


FIG. 20

COMPARATIVE HERBAL PROFILING SHOWS DIFFERENCES AMONG ANTI-INFLAMMATORY HERBS SUCH AS ECHINACEA, ARNICA AND SIBERIAN GINSENG

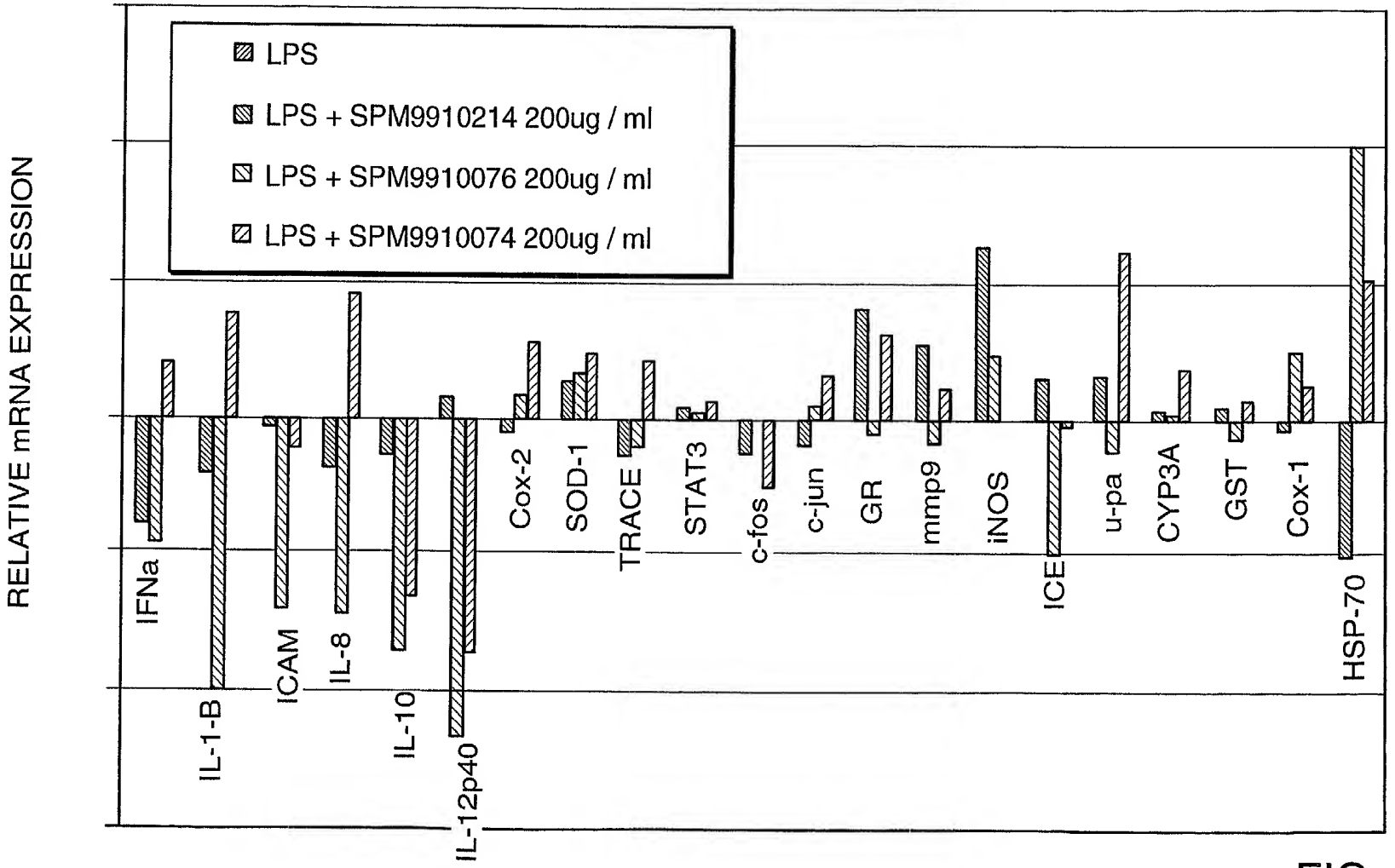


FIG. 21

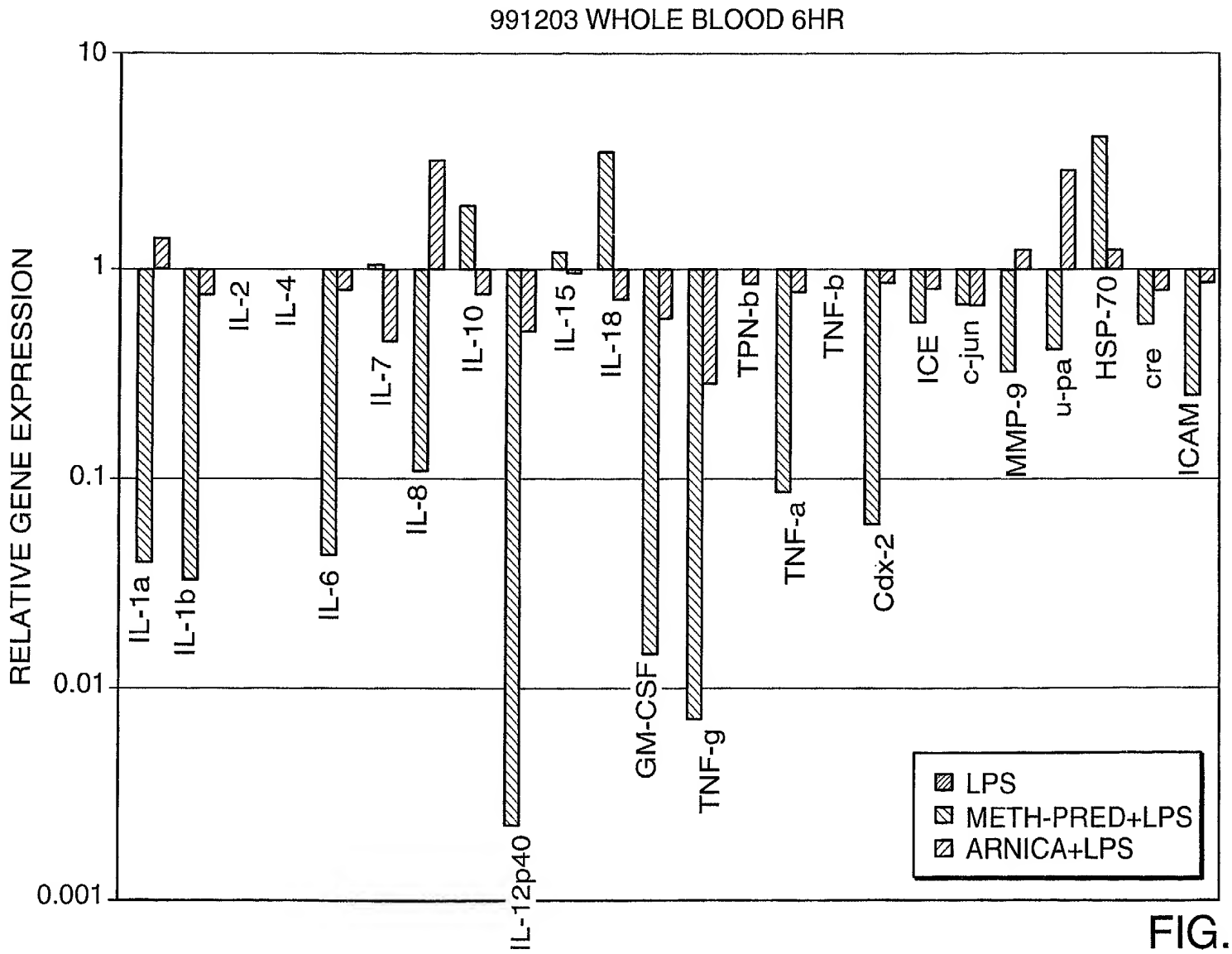


FIG. 22

PRECISION PROFILES CAN CORRELATE WITH A DOSE RESPONSE FOR A GIVEN HERBAL

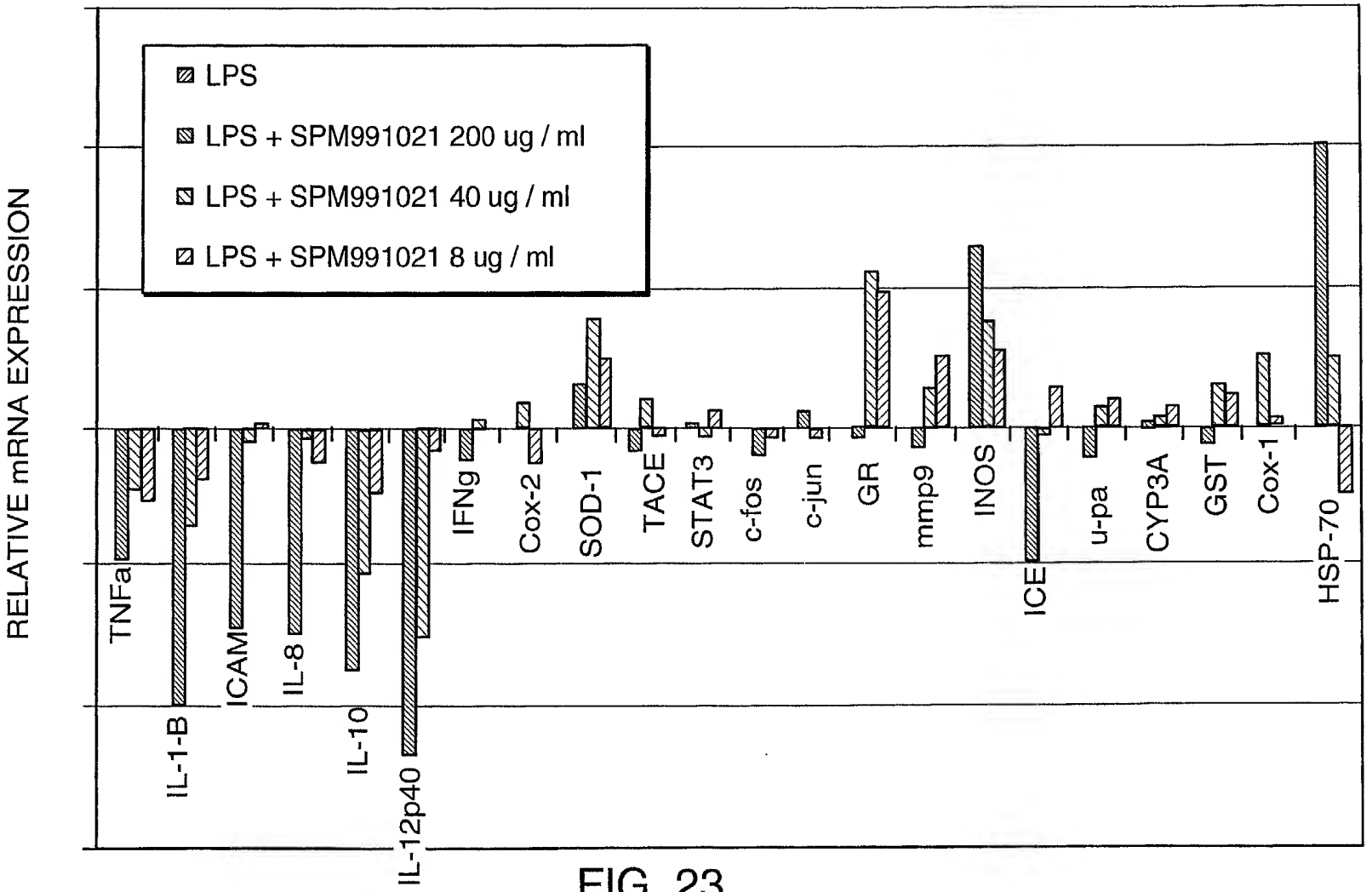


FIG. 23

PRECISION PROFILES REVEAL CONTAMINATION WITH ENDOTOXIN AMONG DIFFERENT COMMERCIAL BRANDS AS REVEALED IN SPM010 AND SPM016

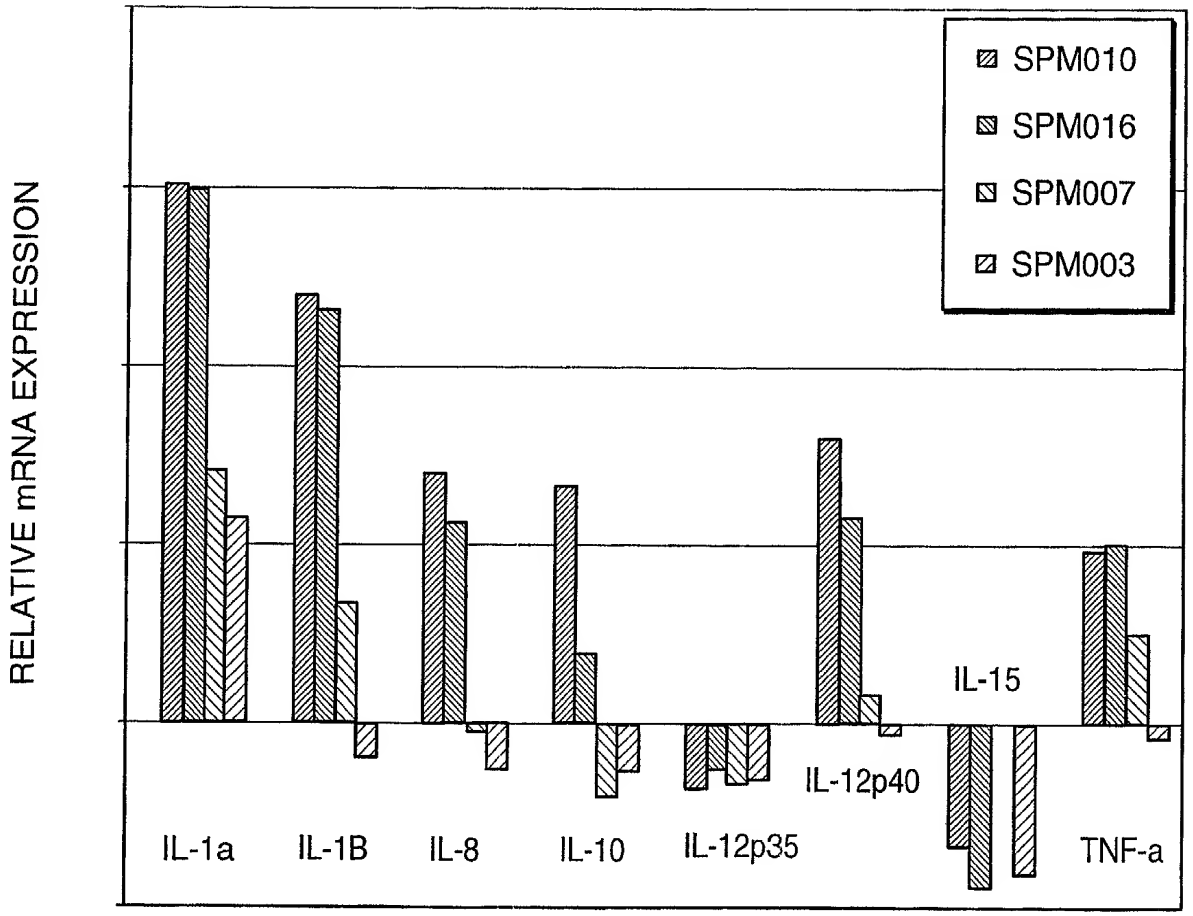


FIG. 24

HIGH DOSE COMPARISON OF UNSTIMULATED THP-1 CELL TREATMENT WITH THREE HERBAL PREPARATIONS SHOWS SIGNIFICANT VARIATION IN EFFICACY

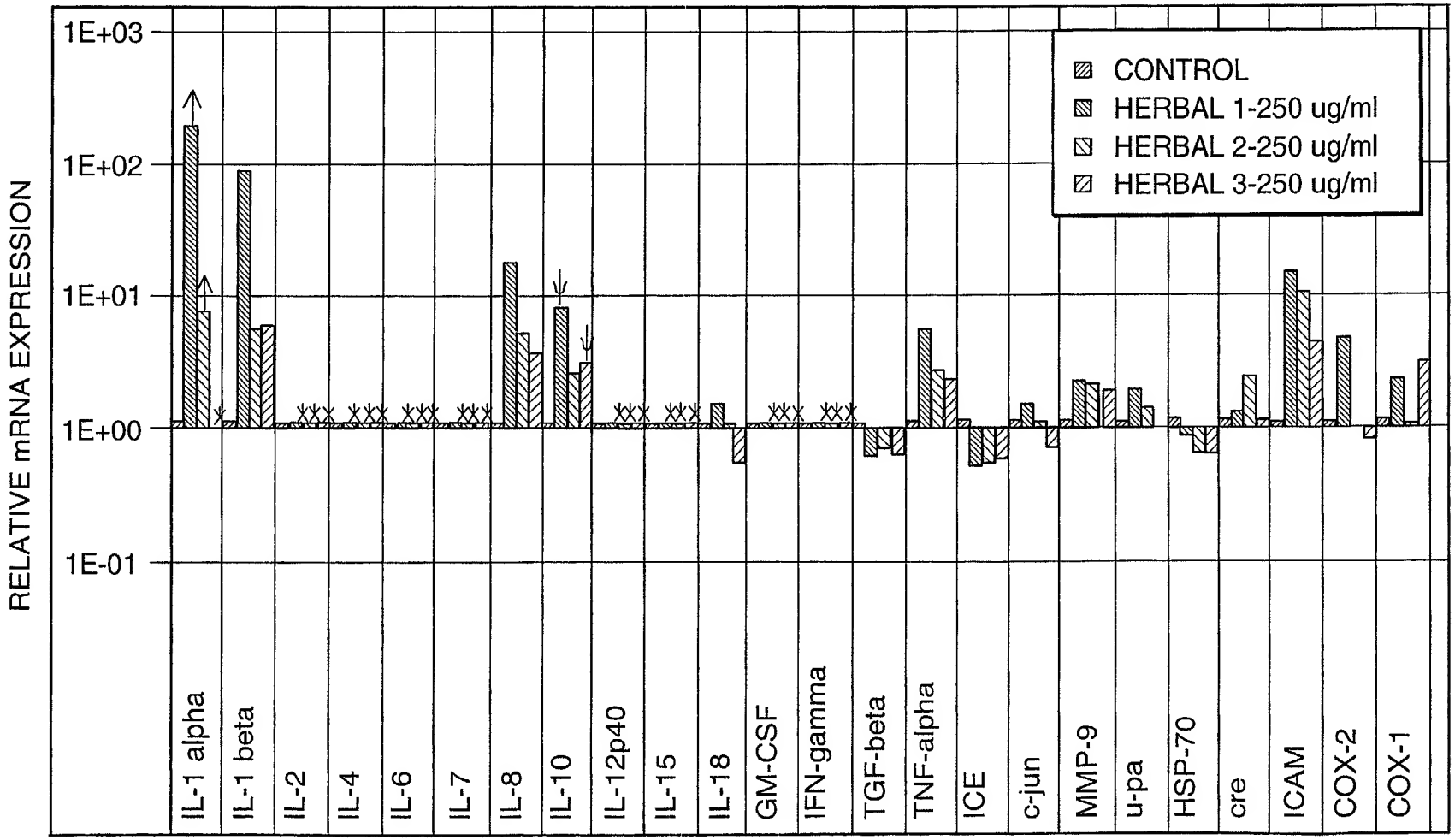


FIG. 25a

TREATMENT OF UNSTIMULATED THP-1 CELLS WITH A SINGLE HERBAL SHOWS A NICE DOSE RESPONSE AMONG A SUBSET OF GENES

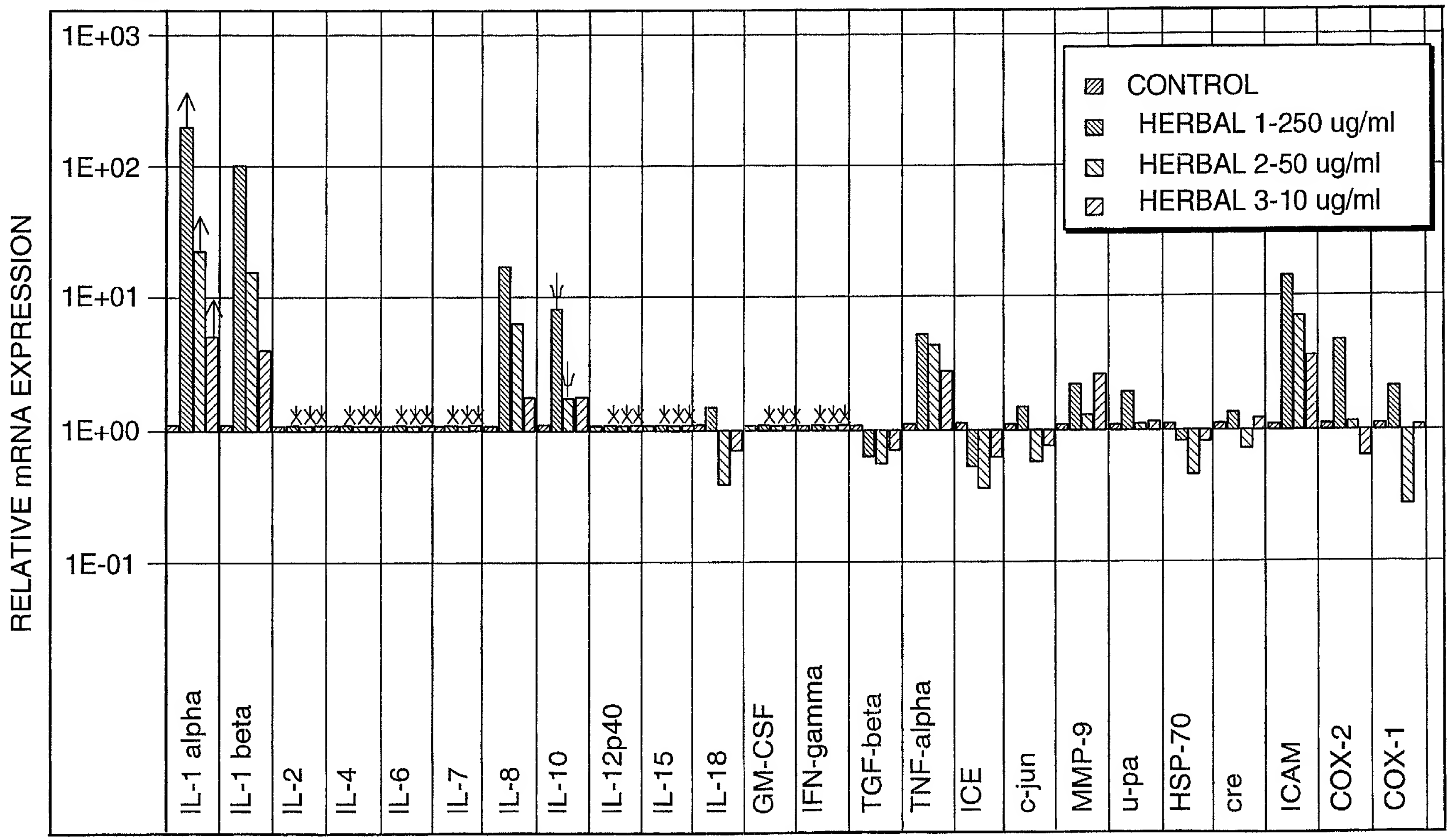


FIG. 25b

PRECISION PROFILES ALLOW FOR COMPARISON OF
COMMERCIAL ECHINACEAS (E1-E4)

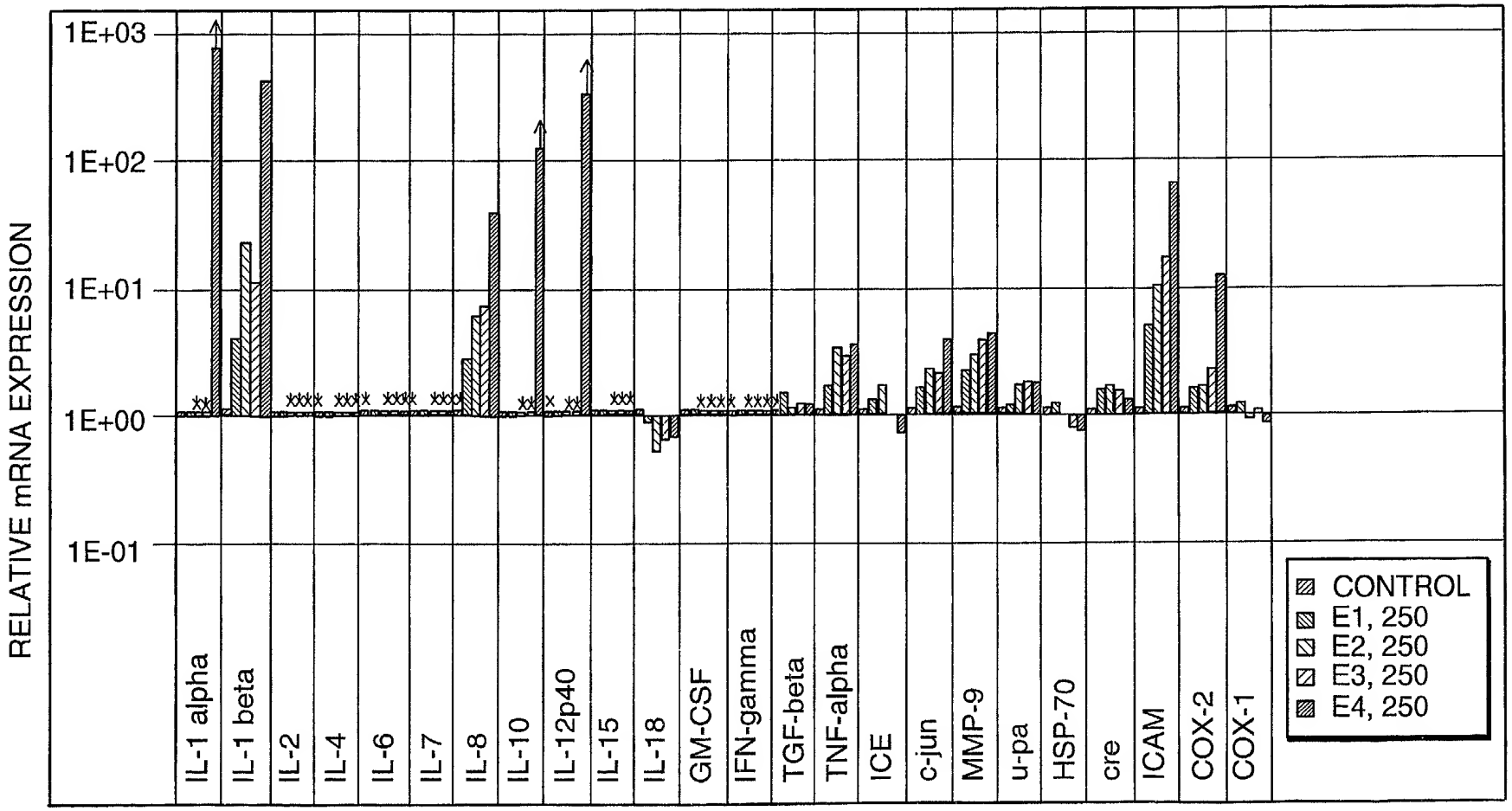


FIG. 25c

Figure 26. Inflammation Precision Panel Subset Demonstrates Steroid Response in 3 Day Study

Relative mRNA Expression

Figure 26(a)

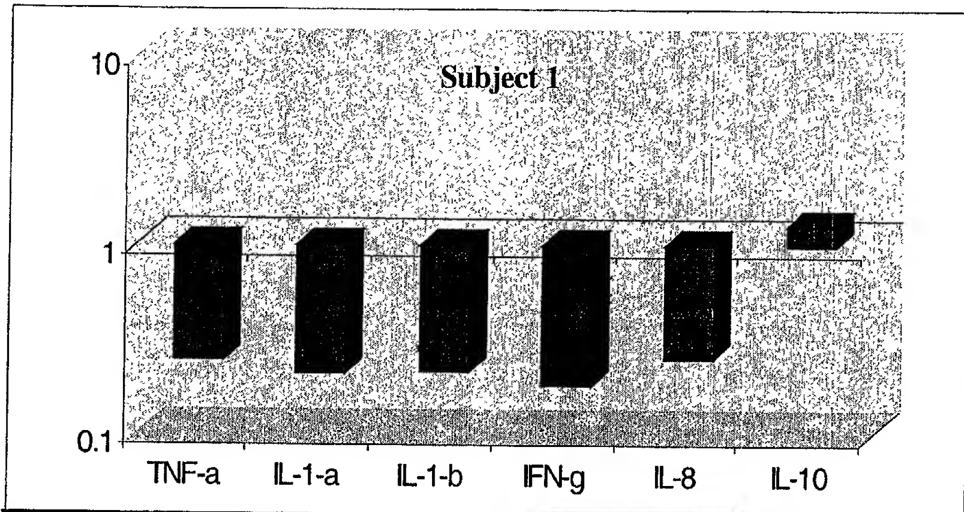
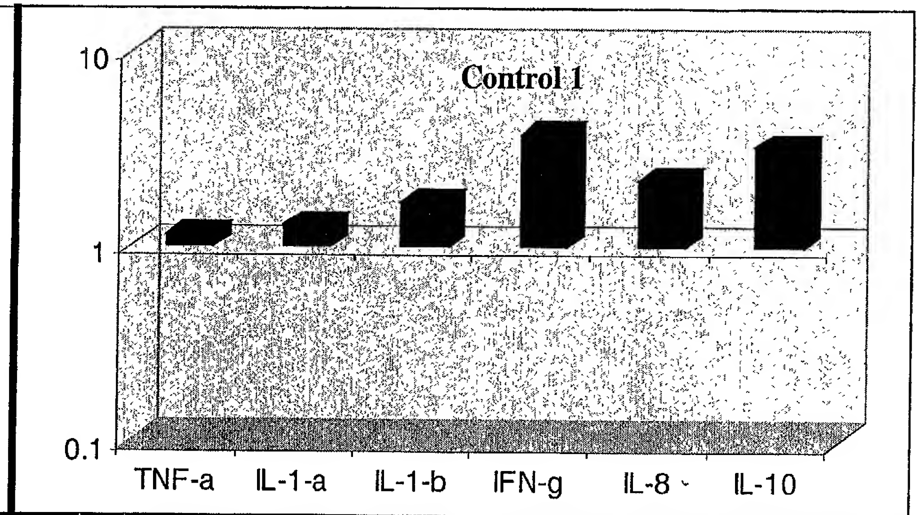


Figure 26(b)



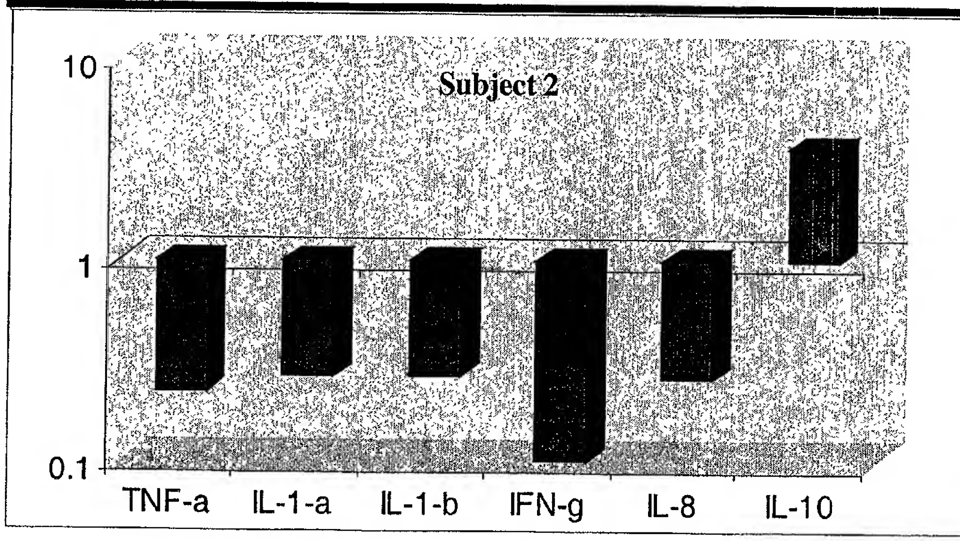


Figure 26(c)

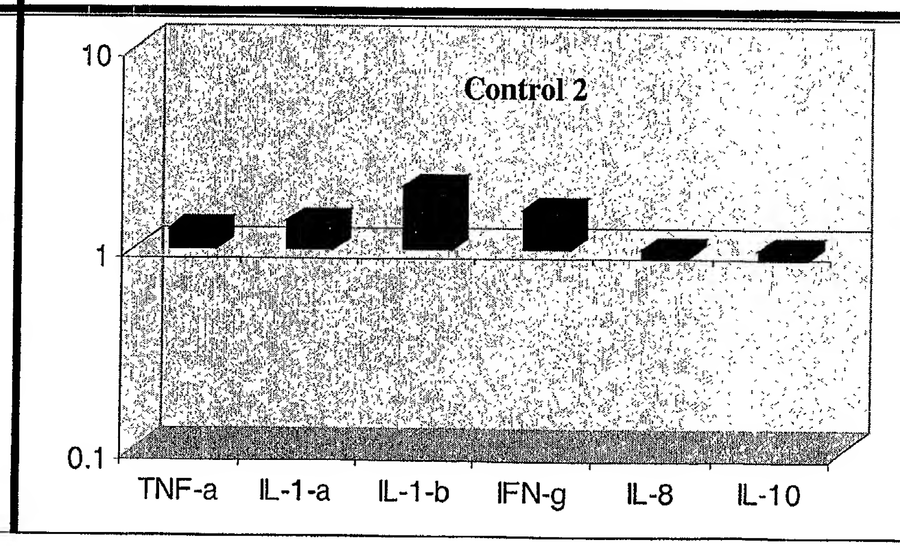


Figure 26(d)

Figure 27. Comparison of Methylprednisone and High-Dose Ibuprofen in Patients Using Inflammation Precision Panel Subset

Figure 27(a) Figure 27(b)

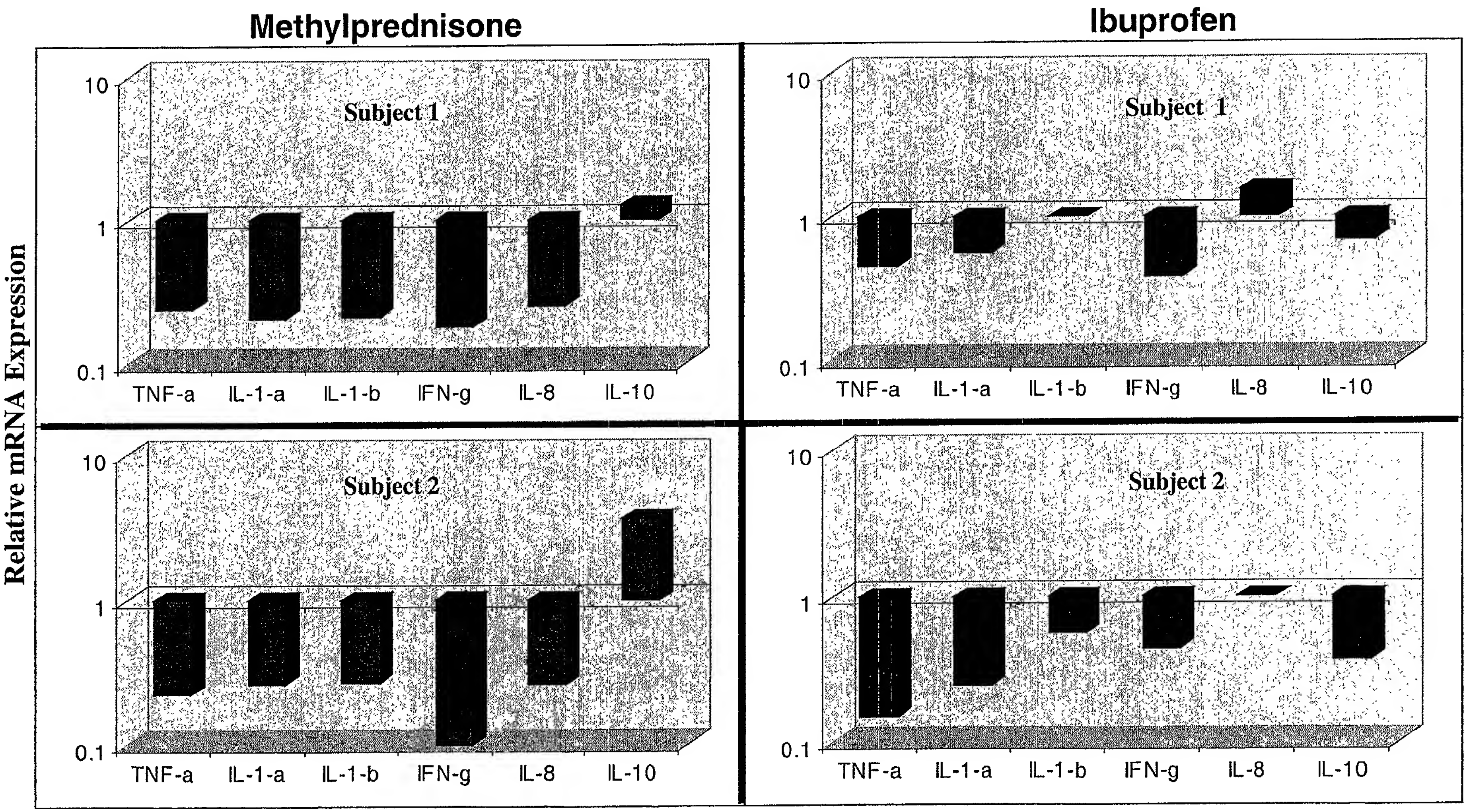


Figure 27(c) Figure 27(d)

Figure 28. Inflammation Precision Panel Subset Identifies COPD Patients

Figure 28(a)

Figure 28(b)

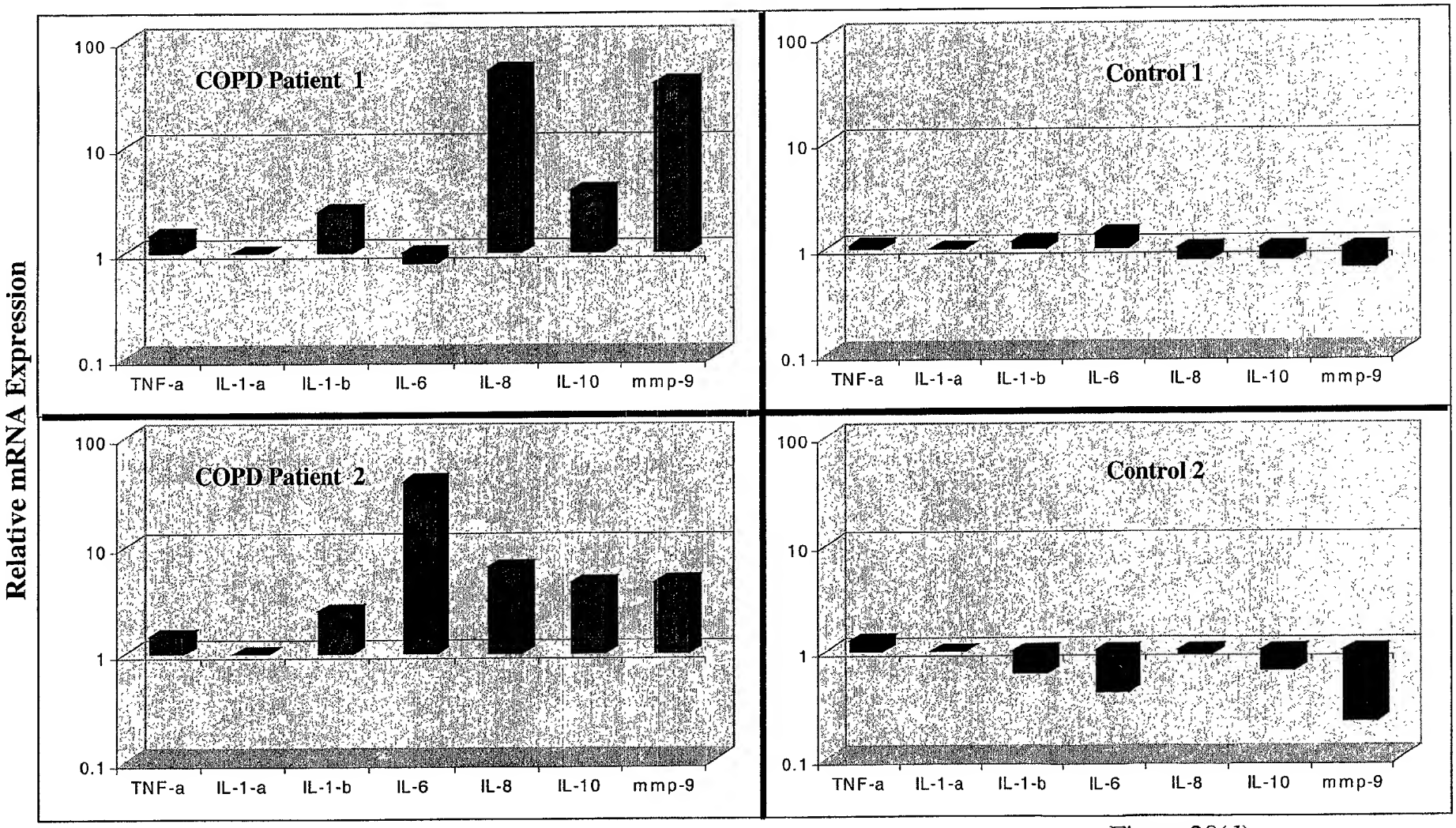


Figure 28(c)

Figure 28(d)

Figure 29(a). Comparison of Calibrated Profile Data Sets (Using Inflammation Precision Panel Subset) After In-vitro and In-vivo drug exposure (Steroids) -- Study 1

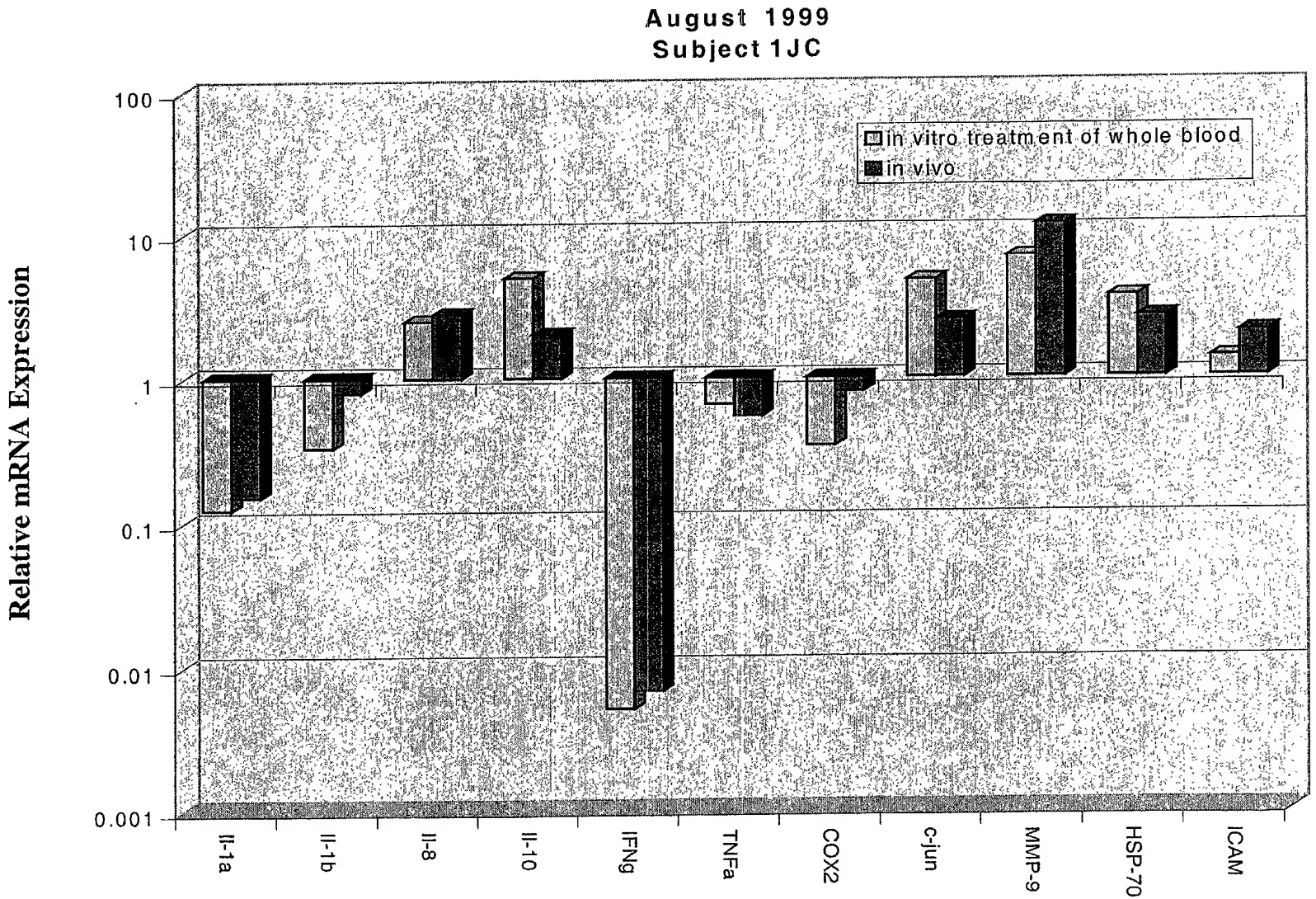


Figure 29(b). Comparison of Calibrated Profile Data Sets (Using Inflammation Precision Panel Subset)
After In-vitro and In-vivo drug exposure (Steroids) -- Study 2

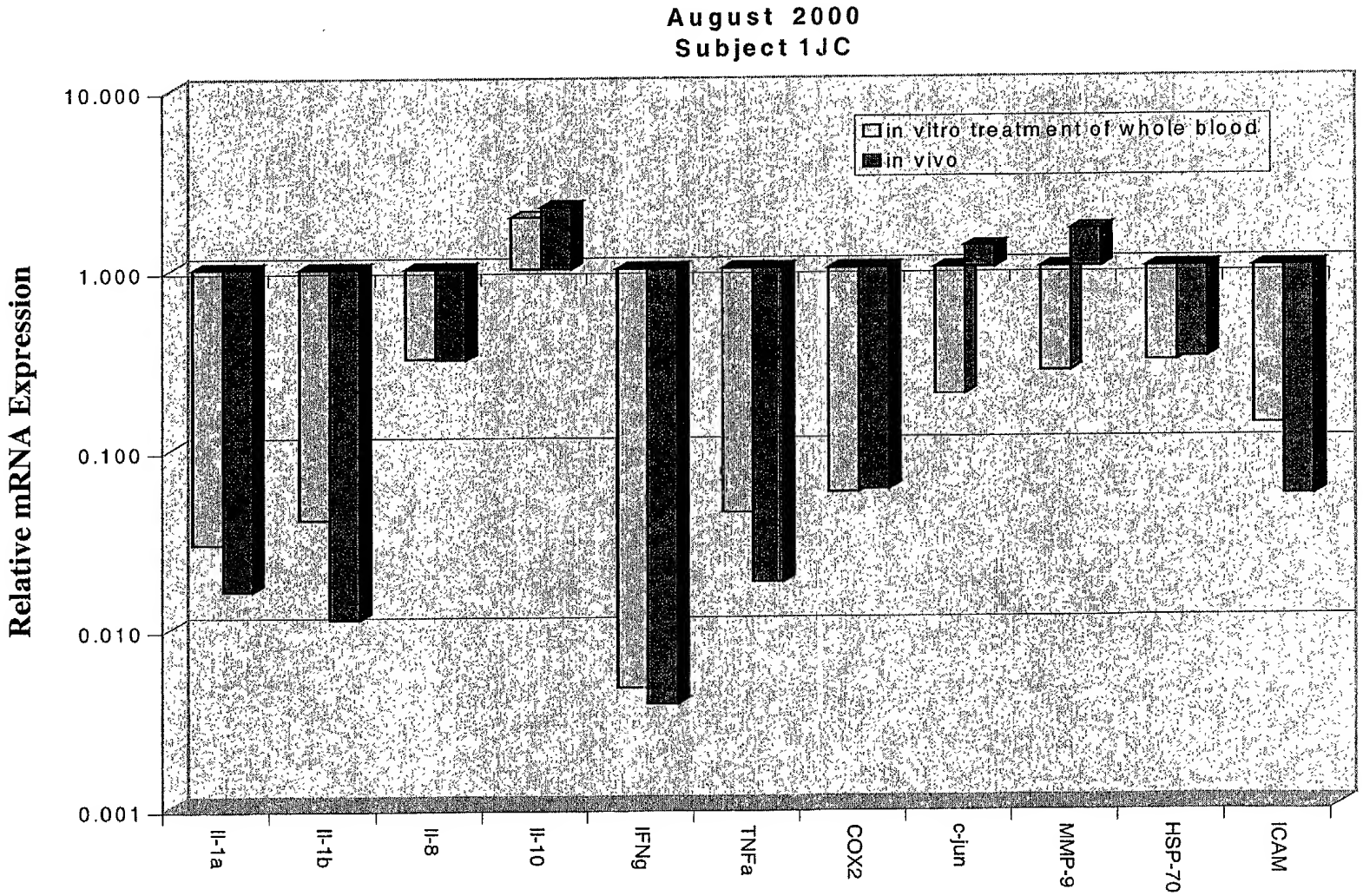


Fig. 30. Effect of different agents evaluated using a subset of the Precision Prostate Panel, and showing broad functions of panel constituents

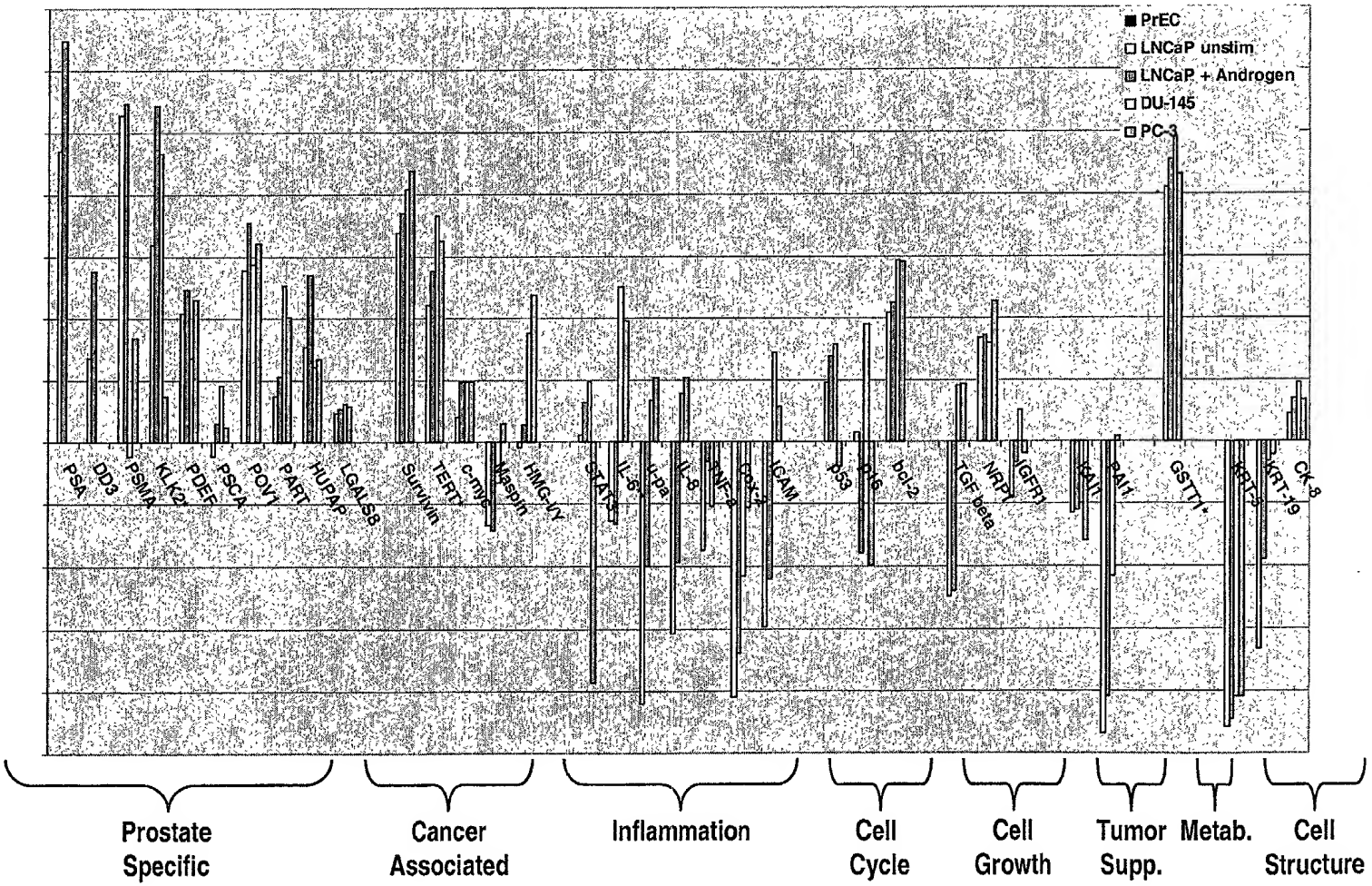


Fig. 31. Effect of the pharmaceutical clofibrate as measured on rat liver metabolism precision panel

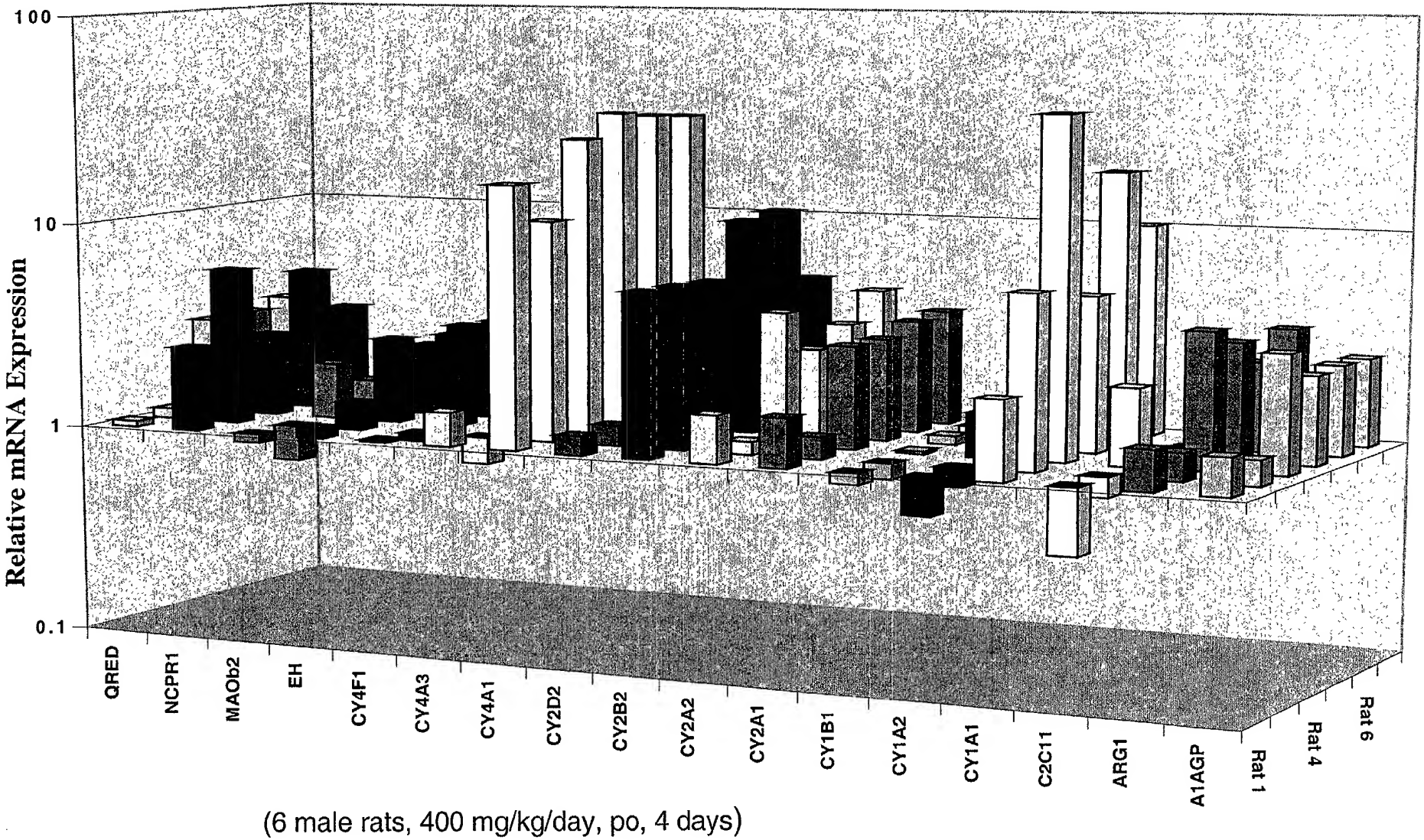


Fig. 32. A metabolism Precision Panel differentiates drug responses in rats.

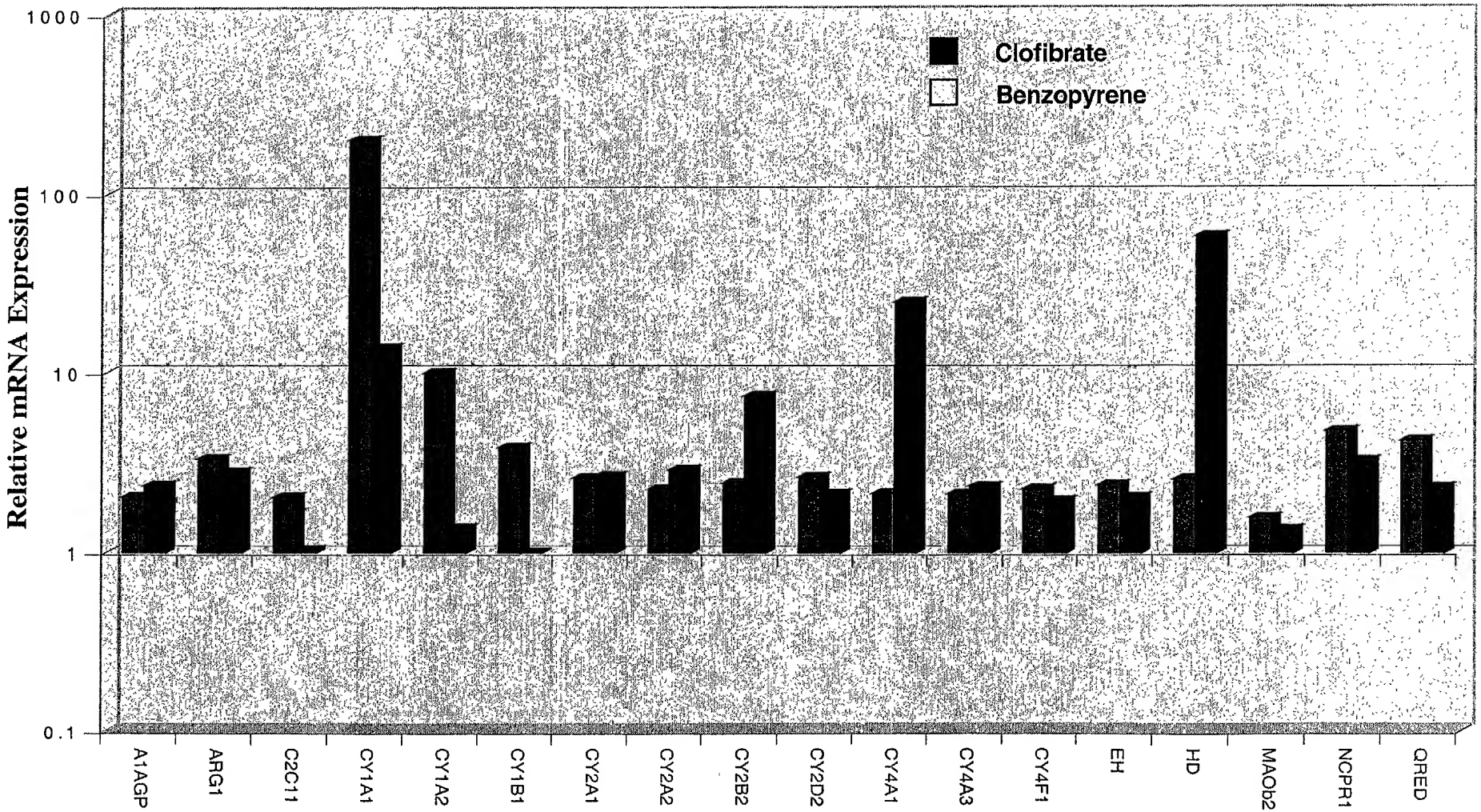


Fig. 33. A combination of the skin/epithelial and vascular precision panels show the effect of administration of a stimulant.

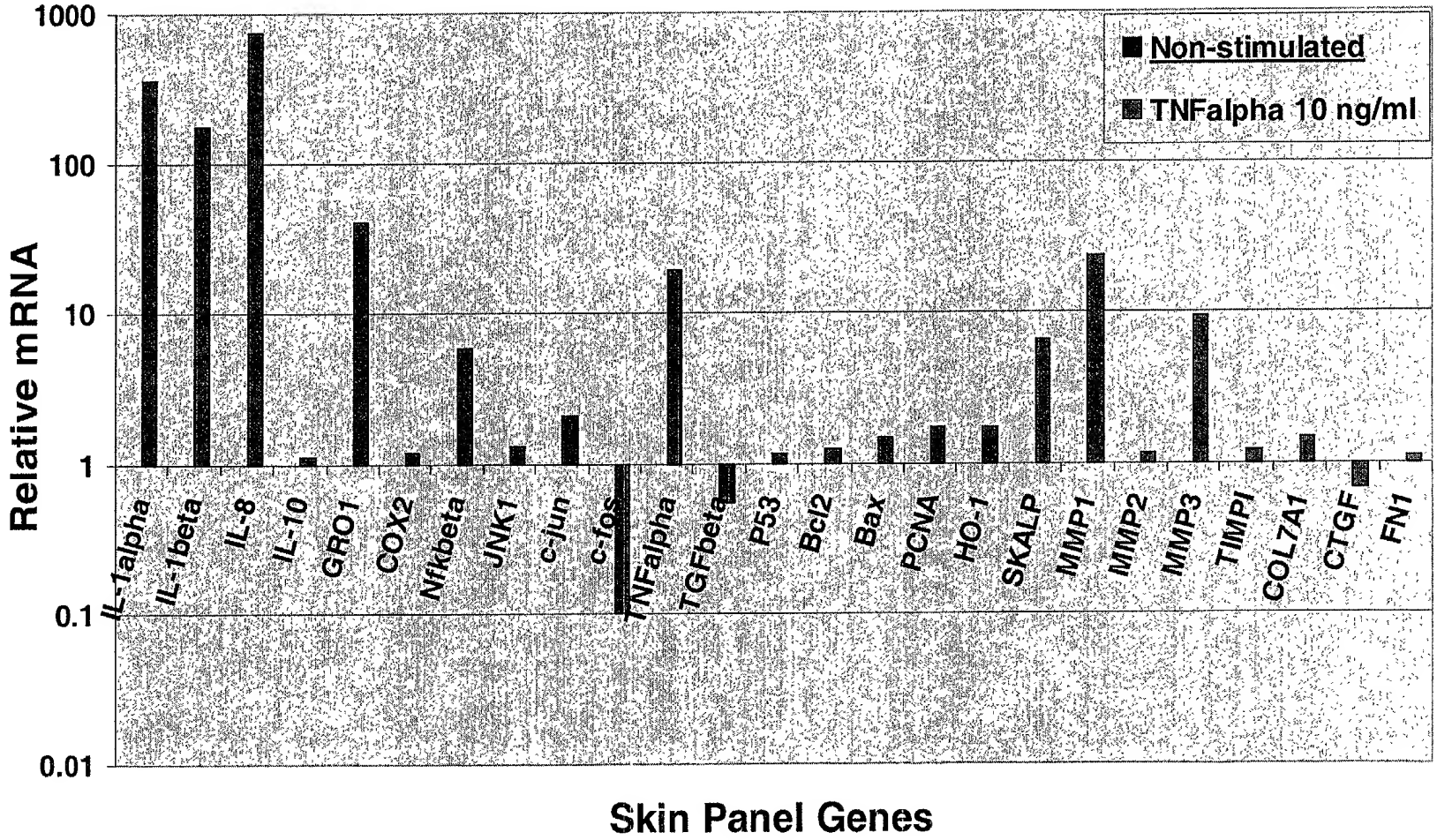


Figure 34: Example use of the human liver precision panel

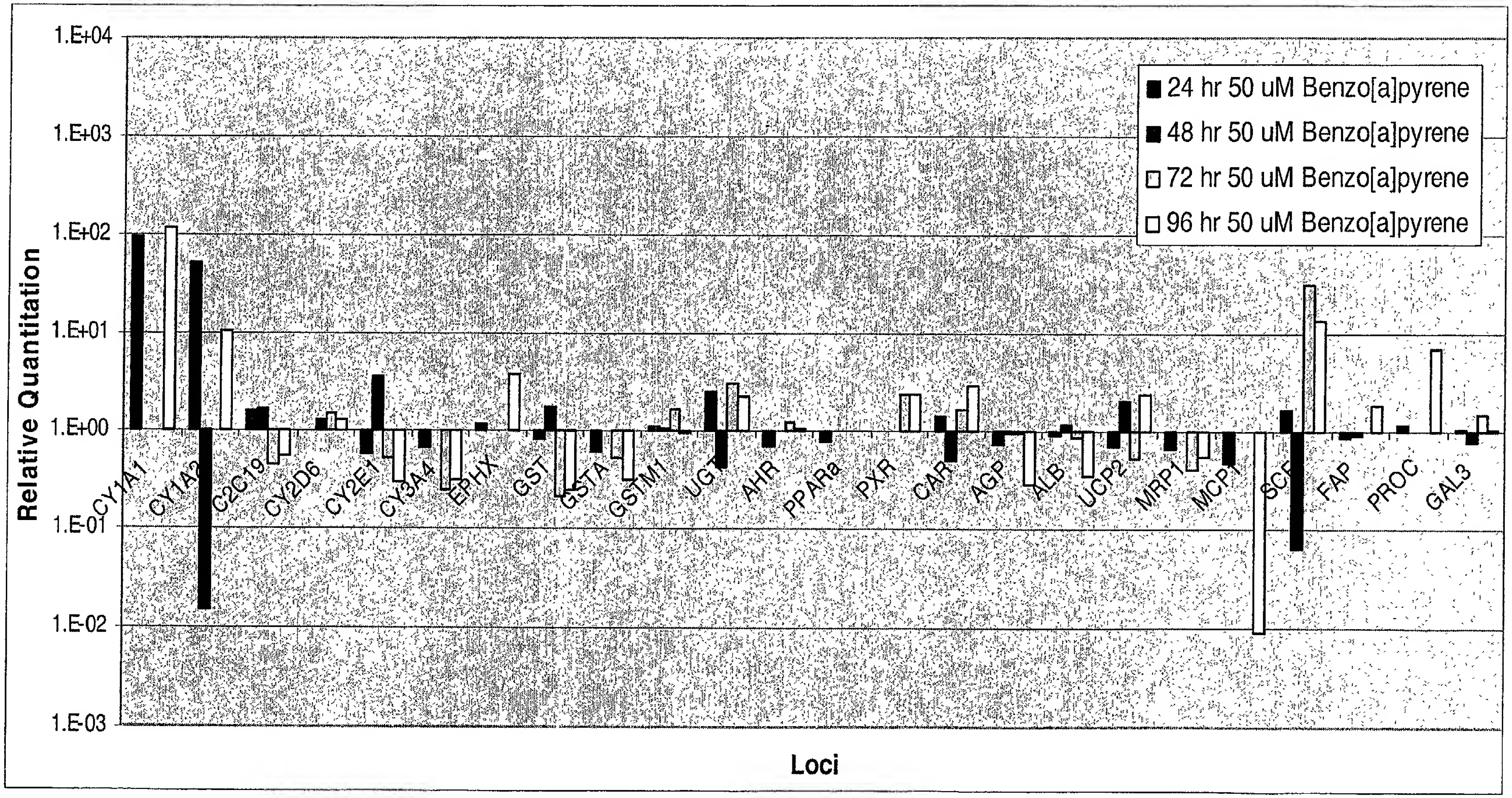


Figure 35. Human umbilical vein cells treated with TNF alpha and assayed on the vascular precision panel

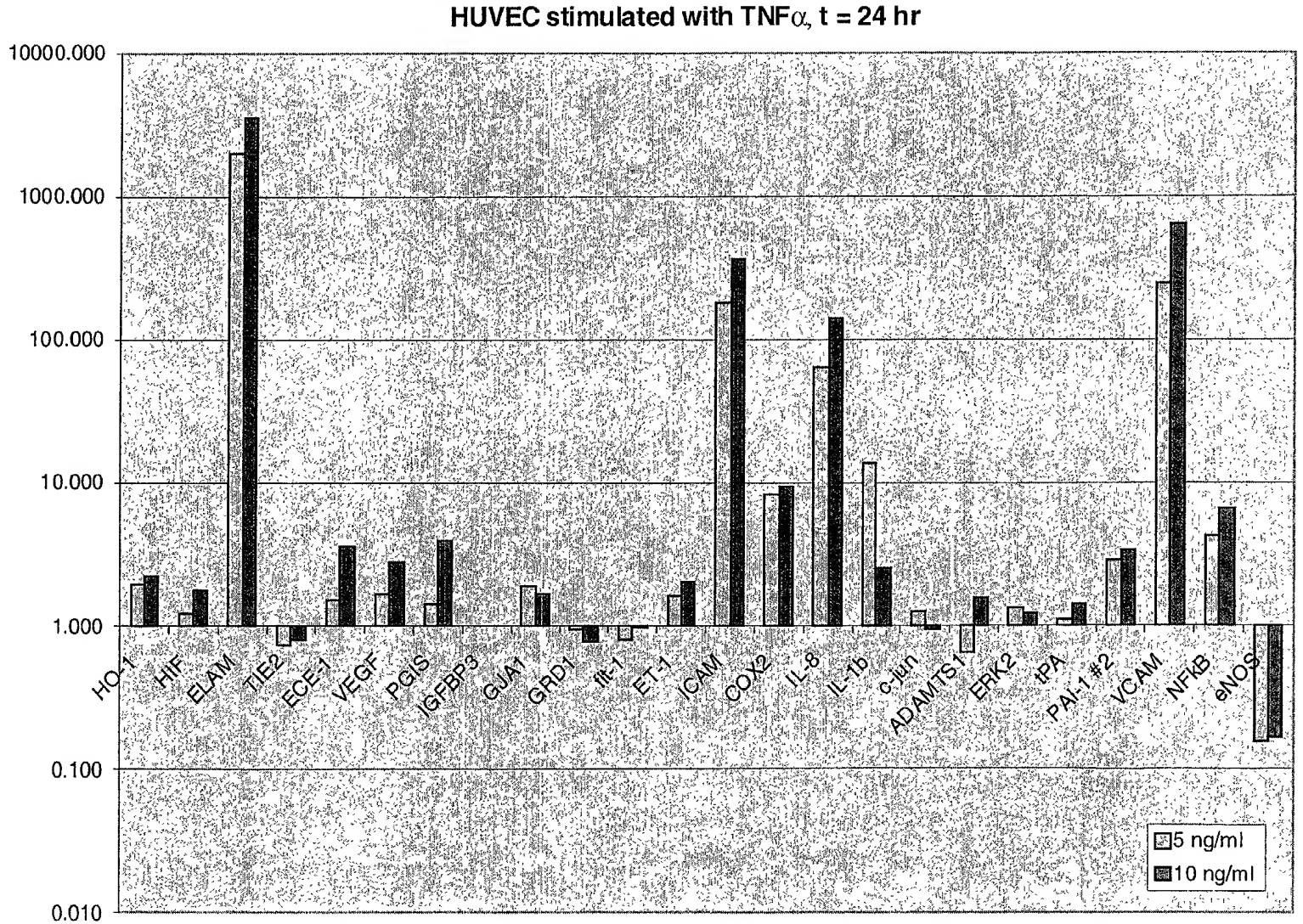


Figure 36. Assay of stimulated, human keratinocytes on the Skin Precision Panel